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British Heart Journal

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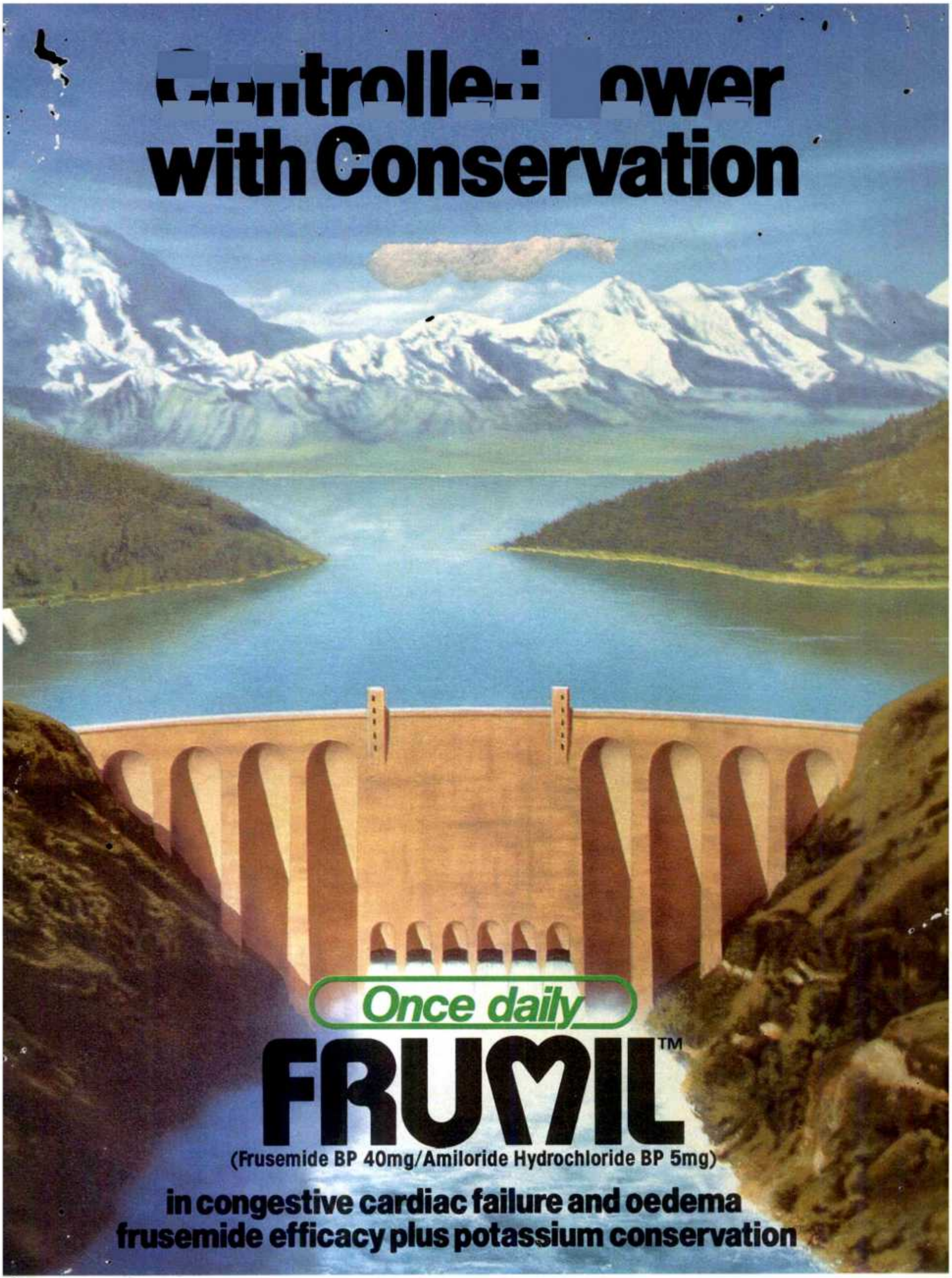

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Editorial

Management of primary pulmonary hypertension

CELIA M OAKLEY
From the Royal Postgraduate Medical School, Hammersmith Hospital, London

When Paul Wood first described primary pulmonary hypertension[1 2] he believed it to have a vasoconstrictive origin and showed that the pulmonary vascular resistance could be selectively lowered in some but not all of these patients by infusion of acetyl choline into the pulmonary artery[3] in contrast to patients with the Eisenmenger syndrome, who were invariably unresponsive.[3 4] The pathogenesis has since been argued, microthromboembolism and thrombosis in situ having some proponents, but the concept of an increased smooth muscle tone perhaps generated by endothelial damage and platelet activity has gained ground. Efforts to find an effective orally active specific pulmonary arteriolar dilator have continued over the years but with little success, though there has been considerable recent resurgence of interest.

Observations made in beef cattle grazing at high altitude and in humans living and exercising at altitude have shown an individual and species variability suggesting a genetically determined hyperreactivity.[5] This pulmonary hypertension is reversible on return to sea level, and the incidence of primary pulmonary hypertension is seemingly higher in populations living at high altitudes.[6] Childhood[7] and familial cases are well known,[8] and an association with Raynaud's phenomenon was early noted.[9]

In the European epidemic of primary pulmonary hypertension, which was linked with the slimming drug aminorex fumarate, only an estimated 0·2% of individuals taking the drug developed the disease and the condition was usually reversible.[10] Primary pulmonary hypertension has also been linked with fenfluramine,[11] an anorectic which is still available. A concept of idiosyncratic pulmonary hypertension of possible dietary origin grew from this experience and from observations of a malignant type of pulmonary hypertension in rats who had eaten seeds of *Crotalaria spectabilis* which contains the alkaloid monocrotaline.[12]

Primary pulmonary hypertension is commoner in women of childbearing age than in any other group, symptoms often develop after puberty or postpartum, and progression of pulmonary vascular disease has been associated with the use of oral contraceptives.[13 14] There is some experimental basis for an association with female hormones,[15] and the use of a non-virilising antioestrogen such as tamoxifen might even find a place in treatment.

The prognosis of primary pulmonary hypertension is grave, though a few patients remain stable without specific treatment and many survive longer than the median two years of Wood's first cases.[16] A clinical diagnosis can often be made, but it is essential that every patient has full cardiac and pulmonary investigations to ensure that no treatable cause of secondary pulmonary hypertension is left undiscovered.

The place of lung biopsy is controversial.[17] It has the academic attraction of aiding prediction of likely vasodilator responsiveness as well as the possibility of uncovering a specific underlying cause. Unfortunately, transbronchial biopsy produces too small a sample, and since haemorrhage or pneumothorax would be especially hazardous in these patients an open lung biopsy is safer but it has not yet been shown to justify itself. Pulmonary veno-occlusive disease can usually be recognised clinically, although lung biopsy provides confirmation of this quickly fatal disorder. Medial hypertrophy in primary pulmonary hypertension appears to precede intimal proliferation, obliterative fibrosis, fibrinoid necrosis, and the "plexiform arteriopathy" of Wagenvoort,[18] but the therapeutic dilemma is how to get hold of patients at a stage of medial hypertrophy before these irreversible changes occur. Symptoms are absent until the disorder is far advanced, and the appearances at necropsy are usually identical to those in the Eisenmenger syndrome.[18] Fanciful wishful thinking suggests that if increased vasomotor tone and reactivity generate more muscle then this muscle will carry more receptors and at an earlier stage might allow a beneficial selective pulmonary vasodilator response to normally non-selective agents. A recent report describes[19] a rare case of a

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man in whom sublingual isoprenaline repeatedly induced a transient fall to normal of a moderately increased pulmonary artery pressure and achieved this in four separate studies over a four year period during six years of clinical benefit, a seemingly clear case of reversible vasoconstrictive pulmonary hypertension. Another reported case showed a dramatic response to acetyl choline, but three years later the pulmonary artery pressure was higher and no longer fell with acetyl choline.[20] These cases, however, differ greatly from most patients with primary pulmonary hypertension, most of whom have higher pulmonary artery pressures when first seen and show at best a much less dramatic response to any drug.[21-24]

Therapeutic endeavour is encouraged by a few patients who have shown spontaneous regression of primary pulmonary hypertension.[25 26] Two reported patients had both developed symptoms in childhood[25] or adolescence,[26] and one had already advanced to a stage of right ventricular failure when death would have been no surprise.[25] This shows that clinically advanced disease should not necessarily be equated with irreversibility. In another personal case regression to normal from pulmonary hypertension at systemic level occurred in a woman who had been treated with an early calcium antagonist, prenylamine, prescribed to her years earlier for angina presumed to be from the right ventricle.

Vasodilator drugs can improve cardiovascular function only in patients with primary pulmonary hypertension who have a high level of reversible vasomotor tone in the pulmonary bed and, conversely, they must have a detrimental effect in patients with irreversible anatomical changes.[22 27] Selective systemic vasodilatation will cause hypotension and may be fatal unless left ventricular filling increases. The right ventricular output is characteristically very low in primary pulmonary hypertension, and it may paradoxically fall further after the chosen vasodilator if the drug either reduces venous return and right ventricular filling pressure or if it has negative inotropic properties and reduces right ventricular contractile force without relieving its afterload. Thus nifedipine has been reported to cause a reduction in cardiac output associated either with a fall in right atrial pressure[28] from systemic vasodilatation or with an increase in right atrial pressure associated with evidence of right ventricular failure.[29] These adverse effects are not apparent when nifedipine unloads the right ventricle by pulmonary vasodilatation and the cardiac output rises.[30 31] In just the same way net benefit from nifedipine has been reported in left ventricular failure.

Patients with a patent foramen ovale were early observed by Wood to have a better prognosis; they can keep the left ventricle filled and are less likely to become hypotensive or to die suddenly. In such patients a favourable response to a drug may be seen by an increase in systemic arterial oxygen content while a fall signals selective systemic vasodilatation with an increase in right to left shunting. Unlike in mitral stenosis successful reduction in pulmonary vascular resistance in primary pulmonary hypertension is not normally associated with a fall in systemic arterial saturation, caused by perfusion of underventilated lung, provided the cardiac output rises.[27] Recruitment of previously unperfused vessels rather than a general relaxation of vasomotor tone may possibly account for some observed rises in cardiac output associated with a fall in both systemic and pulmonary artery pressures. This phenomenon may explain refractory hypotension and death reported with incremental dosage of a drug which had seemed to be well tolerated[27] or there may be rapid attenuation of an initially favourable response.[32] In some patients given a vasodilating inotropic agent such as isoprenaline the pulmonary artery pressure has fallen[33 34]; in others it has caused a rise in right ventricular output with a deleterious rise in pulmonary artery pressure[35] associated with failure to dilate the lung vessels; calculated resistance may stay the same or actually fall, tachycardia is usual, and tremor uncomfortable.

Conflicting responses (many favourable but some adverse) have been reported from acute studies of many different vasodilators either infused into the pulmonary artery or given intravenously: acetyl choline,[4] tolazoline,[36] phentolamine,[37-39] isoprenaline,[33 34] and diazoxide,[40-43] but long term oral treatment has been disappointing. Prostacyclin suggested itself as a suitable drug for acute assessment,[44-46] being a powerful relaxant of vascular smooth muscle, and it may be particularly relevant if abnormal platelet behaviour is important in the pathogenesis of primary pulmonary hypertension. Although non-selective, prostacyclin is easily titrated and can be used safely for assessing drug responsiveness. Since the vasodilator effect of hydralazine is thought to be mediated by endogenous prostaglandins its use in primary pulmonary hypertension was attractive,[47-49] but as with nifedipine both beneficial and serious adverse reactions have been reported. Recently, the use of diltiazem[50 51] and captopril[52 53] have been reported. Diltiazem has the least myocardial depressant effect of the calcium antagonists so is the most attractive for use in primary pulmonary hypertension. Enalapril with its longer action may prove preferable to captopril. New synthetic beta adrenergic agonists such as pirbuterol,[54] with a high selectivity for pulmonary beta$_2$ receptors, will no doubt be "better" than isoprenaline.

Sadly, structural obliteration of the pulmonary circulation is probably the major factor by the time most patients are seen, but even if only 5% or 10% of patients are capable of pulmonary vasodilatation every patient with primary pulmonary hypertension should be given the benefit of an inpatient, invasive, acute haemodynamic assessment. There is yet no guide to the agent of choice. Positive responders probably respond to each of the drugs, and those few more fortunate patients stand to gain a great deal from long term treatment. There is no role for digitalis in patients with sinus rhythm, and diuretic dosage should be minimal. Oral anticoagulants should usually be given to prevent secondary thromboembolism as in other low output states. Oxygen inhalation[55] at home aided by an oxygen condenser may be beneficial in some. Portable oxygen is helpful for patients with arterial desaturation. Patients with primary pulmonary hypertension should be screened for evidence of collagen vascular disease, but it is even more important for patients who present with symptoms of a connective tissue disorder to be investigated for pulmonary hypertension at a time when vasodilator treatment may be most rewarding; they are patients with systemic lupus erythematosus[56] or scleroderma,[57] particularly in the CREST syndrome or mixed connective tissue disorder and rheumatoid disease.[58] Patients with systemic lupus erythematosus who are found to have the lupus anticoagulant should be early suspects for pulmonary hypertension; it is of interest that nifedipine is the usual drug of choice for the treatment of Raynaud's phenomenon and might be preventing the development or progression of associated pulmonary hypertension in some of these patients.

Heart and lung transplantation is the final radical treatment for pulmonary vascular disease in primary pulmonary hypertension and the Eisenmenger syndrome and may offer the only realistic hope for palliation of advanced disease.

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Br Heart J 1985; 53: 5–8

Review

Reduction of infarct size
An attractive concept: useful— or possible— in humans?

W KÜBLER, A DOOREY*

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The extent of myocardial infarction—that is, the amount of necrotic myocardial tissue—is a main determinant of early and late prognosis in patients with acute myocardial infarction.[1]

A vast number of animal experiments have been carried out in this field which have greatly contributed to our understanding of myocardial infarction, infarct extension, and the resulting haemodynamic, metabolic, and electrophysiological consequences. In addition, several careful clinical studies have been carried out. Despite these efforts spanning more than a decade, there is still no generally accepted method of reducing infarct size that is available for routine clinical use. Apart from the methodological problems of such research this dilemma seems to be predominantly due to biological, and especially metabolic, problems, which are discussed briefly in this paper.

Reduction in infarct size has been sought through many different approaches. In essence, they can be classified according to three main aims: (*a*) the reduction of myocardial energy demands; (*b*) the stimulation of glycolytic energy production; and (*c*) reperfusion in order to re-establish the blood supply and hence oxygen availability.

Reduction of myocardial energy demands

Although for varied reasons the results of many experimental infarct reduction studies are controversial, it is nowadays widely accepted that reduction in myocardial energy demands by the administration of beta blockers, nitrates, or calcium antagonists can lead to a delay in the development of irreversible ischaemic damage in the affected area.[2 3]

It seems doubtful, however, that these positive results from animal experimentation can also be expected to apply to the clinical situation of a patient with acute myocardial infarction. According to enzyme distribution patterns and metabolic profiles of high energy phosphates and glycolytic intermediates in early ischaemia, energy metabolism in the ischaemic human myocardium follows the same principles as, for example, in the canine heart.[4] During the early phase of ischaemia mainly creatine phosphate (CP) breaks down, coincident with and probably closely related to the development of diastolic pump failure.[5] This decline in CP can be ameliorated by a reduction in myocardial energy demands—for example, by cardioplegia.[6] In the beating heart in situ, however, this period during which amelioration is possible lasts for only a few minutes. Thereafter the energy deficit in ischaemic myocardium—that is, net adenosine triphosphate (ATP) breakdown—can be influenced by a reduction in myocardial energy demands only to a very minor degree.[6] As a patient with acute myocardial infarction will generally be under medical care at the earliest 30–60 minutes after the onset of symptoms—that is, after the onset of myocardial ischaemia—probably all interventions used to delay the infarcting process can be instituted only after CP breakdown has appreciably progressed. The effect of these interventions, therefore, has to be presumed to be greatly attenuated.

Although the experimental results have not always been convincingly positive, and the foregoing theoretical considerations even suggest an attenuated effect in patients, several well conducted studies in humans indicate a reduction in infarct size after the administration of beta blockers[7–9] or nitrates.[10] In evaluating these results reduced enzyme washout from the infarcting area (underestimation of infarct size), consequent to pharmacologically reduced energy demands and hence reduced perfusion in and around the ischaemic zone, has to be taken into account. At least one study included non-enzymatic (electrocardiographic) criteria of infarct size as well.[9]

Stimulation of anaerobic energy production

Insufficient myocardial oxygen supply leads via the

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pasteur effect to an activation of anaerobic glycolytic energy production. Based on the activities of glycolytic enzymes in the human or canine heart—as assessed in vitro under nearly "optimal" conditions—glycolytic rates of flux could be expected to be sufficient to cover myocardial energy demands under ischaemic conditions. In vivo, however, such high rates of flux have never been measured, especially not during ischaemic conditions. This is due to the multistage regulation and control of the glycolytic chain. (This control of the metabolic chain is of great physiological importance, since it enables almost instantaneous adaptation of the rate of flux to the actual energy demands.) The main regulatory effectors, apart from some glycolytic intermediates and the ratio of nicotinamide adenine dinucleotide (NAD) to NADH (the reduced form), are the nucleotide phosphates, such as ATP, adenosine diphosphate (ADP), and adenosine monophosphate adenylic acid (AMP), inorganic phosphate, and the pH.[6]

The fall in the concentration of the high energy phosphates, such as CP and ATP, in the ischaemic myocardium can be slowed down by the reduction in myocardial energy demands. This, however, leads to a proportional reduction in the glycolytic flux due to the multistage control of this metabolic chain.[6]

In practice, stimulation of anaerobic glycolytic energy production has been achieved only by preventing or reducing intracellular acidosis by the application of buffer substances.[11] Such a buffer—for example, histidine—should be able rapidly to penetrate into the intracellular space, a prerequisite which cannot be adequately fulfilled under ischaemic conditions, as the buffer probably cannot be brought to the ischaemic area in sufficient concentration.

In order to stimulate glycolytic flux, the administration of substrates for glycolytic energy production—such as glucose—has been advocated, usually in combination with insulin and potassium.[12] Even if the problem of bringing sufficient amounts of glucose to the ischaemic area could be obviated, this therapeutic approach would still probably not be very rewarding. Because of the multistage control of the glycolytic pathway its overall rate of flux is not determined by the concentration of the main substrates, free glucose and glycogen. In the ischaemic canine heart, for example, free glucose is extensively metabolised only during the very early stages, and thereafter glycogen serves as a glycolytic substrate almost exclusively, as free glucose utilisation is blocked at the hexokinase reaction owing to accumulation of glucose-6-phosphate, as a consequence of the rate limiting step at the phosphofructokinase reaction. At this time glucose concentrations even increase owing to debranching of the glycogen tree. At least in the ischaemic canine myocardium, glycolytic flux stops despite sufficient myocardial contents of glycogen and glucose. This halt of glycolytic flux occurs at the level of the phosphofructokinase reaction and is probably due to the lack of ATP for the phosphorylation of fructose-6-phosphate to fructose-1, 6-diphosphate.[6]

The main beneficial effect of glucose-insulin-potassium administration may be the subsequent reduction in plasma free fatty acid concentrations, substances which can increase myocardial oxygen consumption[13] and which may also exert an arrhythmogenic effect.[14 15]

Early reperfusion to re-establish blood supply and hence oxygen availability

The most critical substrate lacking in infarcting myocardium is oxygen, which becomes rate limiting for oxydative phosphorylation at very low values—that is, <1 mm Hg (critical oxygen tension). Hence, oxydative phosphorylation falls precipitously as oxygen tension declines to this range. As a consequence, for a given myocardial cell a situation of partly aerobic and partly anaerobic energy production seems to be rather unlikely. This view is supported by observations in monolayers of cultured heart cells, whose function and high energy phosphate concentrations decline sharply with decreasing oxygen tension below a critical value.[16 17] Thus early reperfusion to re-establish blood supply and oxygen availability is probably the most promising approach to infarct reduction. Pertinent attempts began almost 20 years ago with intravenous administration of streptokinase. The generally negative results of these studies could probably be related in part to an excessive ischaemic period. A delay of 12–72 hours was usually allowed between the onset of symptoms and the start of treatment. This time lag is probably sufficient to induce irreversible ischaemic myocardial damage.

Thrombolytic treatment has again received great interest after Rentrop *et al* reported on its intracoronary use in patients with acute myocardial infarction.[18 19] This form of treatment had been first tried by Chazov *et al.*[20] It is now well established that with the intracoronary administration of streptokinase an occluded "infarct" vessel can be reopened in 70–90% of patients. In fact almost every centre which uses this form of treatment has found that in some patients after thrombolytic reopening of the infarct vessel a dramatic improvement occurs in left ventricular function, the electrocardiogram reverts to normal, low creatine kinase values develop in plasma, and the perfusion defect in thallium-201 scintigrams disappears. Even though observations in individual patients have been so encouraging, however, the overall benefit of this form of treatment has not been firmly established despite a large number of clinical trials.[21] Four controlled randomised trials have yielded conflicting results, two being positive[22 23] and the other two negative.[24-26] The failure consistently to confirm the efficacy of such a theoretically promising technique may be attributed to any of three different causes: *(a)* the treatment may be harmful in some patients, *(b)* it may not be effective or of only marginal effectiveness in most patients, or *(c)* the protocols of the studies have been far from optimal—for example, the acceptance of an excessive ischaemic period.

HARMFUL EFFECTS

The possible hazards of thrombolytic treatment include mainly haemorrhagic complications and complications due to the invasive procedure. Haemorrhagic complications occur in as many as 10% of cases, but a fatal outcome that can be attributed to the intervention occurs in <1%.[27 28]

The myocardial complications due to thrombolytic treatment are probably less serious. They include the occurrence of reperfusion arrhythmias (which are surprisingly benign in humans),[29 30] myocardial haemorrhage (generally restricted to the necrotic zone),[31] and myocardial damage due to calcium overload (occurring predominantly in already irreversibly damaged areas).[32-35] Thus reperfusion may accelerate the necrobiotic process but does not induce additional irreversible myocardial damage.

BENEFICIAL EFFECTS

The beneficial effects of thrombolytic treatment in acute myocardial infarction depend mainly on two factors: *(a)* the duration of ischaemia in the affected area, and *(b)* the residual blood supply allowed by subtotal occlusion of the infarct vessel or the presence of collaterals or both.[36] As this residual flow cannot be assessed by non-invasive techniques, the limits of an ischaemic period that still allows successful reperfusion (that is, reduction in infarct size) cannot be given. As a rule of thumb the following criteria may favour reperfusion: *(a)* anginal pain for more than 10–15 min but not exceeding 3–4 hours; *(b)* ST elevation (>1 mm in leads I, II, and III) (>2 mm in leads V1–V6); *(c)* creatine kinase values still within normal limits; and *(d)* no contraindications (advanced age, haemorrhagic disorders, known malignancy, etc).

From the foregoing discussion it should be obvious that to improve the functional results of reperfusion, shortening of the ischaemic period should always be a primary aim. The ischaemic period can be shortened either by accelerating transport of the patient to hospital or by accelerating the process of reopening the infarct vessel or both. When the intracoronary route of thrombolysis administration is used a major delay often cannot be avoided while the cardiac catheterisation laboratory is being prepared. During this time intravenous infusion of streptokinase could be started immediately after informed consent has been obtained from the patient. At coronary angiography 45% of the infarct vessels are open after this treatment, and a further 25–35% of infarct vessels may be subsequently reopened by the intracoronary administration of streptokinase. In this way the functional results of thrombolysis in acute myocardial infarction could be improved.[37]

After reperfusion of the infarct vessel has been achieved, reocclusion occurs in about 10–25% of cases during the hospital stay.[27 38] This high reocclusion rate would indicate the consideration of subsequent revascularisation procedures, such as angioplasy or bypass surgery or both. These procedures, however, entail added risks, and their use should at least be based on a potential beneficial effect—that is, the presence of salvaged myocardium in the perfusion area of the reopened vessel. The following criteria may favour subsequent revascularisation: *(a)* recurrence of anginal pain; *(b)* no new Q waves on the electrocardiogram; *(c)* a moderate increase in creatine kinase activity in plasma (<1000 IU/l); *(d)* a pronounced reduction in the thallium-201 perfusion defect after reperfusion; and *(e)* no contraindications. By applying such criteria revascularisation of irreversibly damaged myocardial tissue—a procedure of doubtful benefit at best—may be prevented.

Conclusions

The reduction of myocardial infarct size is a concept of great potential clinical importance. At present, the reopening of an occluded infarct vessel by thrombolysis seems to be the most promising approach. Although clearly effective in some patients, the general benefit of thrombolytic treatment in acute myocardial infarction has not yet been definitively established. Before this procedure can be finally evaluated the patients who may benefit may have to be more clearly identified, the procedure itself may have to be improved to reduce the ischaemic period of the infarcting myocardium and thus delay ischaemic damage, and criteria for subsequent revascularisation procedures have to be established. The final evaluation thus has to be based on randomised controlled clinical trials.

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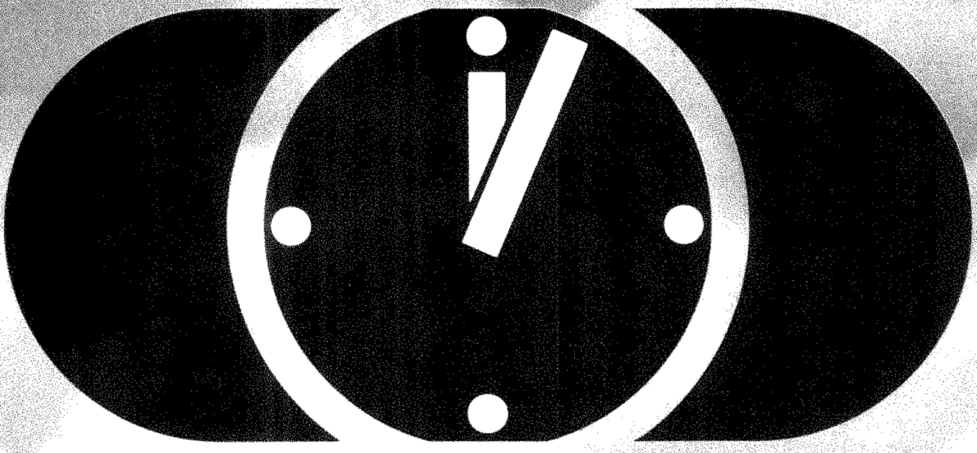

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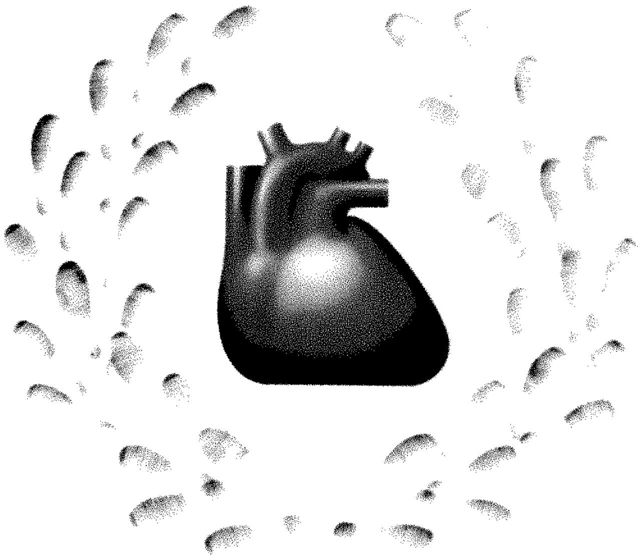

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Quantitative influence of serum creatine kinase isoenzyme MB estimated infarct size and other prognostic variables on one year mortality after acute myocardial infarction

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SUMMARY The aim of the present study was to determine the strength of the relation between serum creatine kinase isoenzyme MB estimated infarct size, other prognostic variables, and mortality after acute myocardial infarction. Serum creatine kinase MB estimated infarct size and 11 other prognostic variables were obtained in 317 patients. By Cox regression analysis the prognostic variables significantly related to mortality were identified: congestive heart failure, estimated infarct size, New York Heart Association class, number of previous infarcts, and age. Congestive heart failure and estimated infarct size were most strongly related to mortality. The relation between the prognostic variables and mortality was non-linear, and the variables influenced each others' relation to mortality. A prognostic index based on all five prognostic variables provided the best means of estimating the probability of survival after acute myocardial infarct. Neither serum creatine kinase MB estimated infarct size nor any of the other prognostic variables had a significant independent influence on mortality, and the probability of survival was high in the absence of any of the prognostic variables in combination.

During recent years methods for the in vivo estimation of infarct size have been developed since the extent of an acute myocardial infarct influences prognosis.[1 2] Methods of estimating infarct size based on serial serum creatine kinase and creatine kinase isoenzyme MB activities correlate closely with the extent of necrosis measured at necropsy.[3 4] Creatine kinase isoenzyme MB estimated infarct size has also correlated well with several indirect measures of infarct size, such as angiographic estimates of left ventricular asynergy and ejection fraction,[5] precordial mapping of Q wave and ST segment changes,[6] and myocardial positron emission tomography with carbon-11-labelled palmitate.[7]

A few studies have compared enzymatically estimated infarct size with mortality and morbidity due to acute myocardial infarction. Patients with such complications as heart failure, cardiac arrhythmias, or early or late death had generally larger infarcts than those without.[2 8 9] Furthermore, when groups of patients were stratified by estimated infarct size a significant positive relation was found between both creatine kinase isoenzyme MB and creatine kinase estimated infarct size and these complications.[8 10–12]

Several studies have identified various prognostic variables for mortality after acute infarction. Nevertheless, no data are available on (*a*) the strength of the relation between mortality and different infarct size, (*b*) the relation between estimated infarct size and other prognostic variables, and (*c*) the influence of other prognostic variables on the relation between estimated infarct size and mortality. The aim of the present study was to evaluate these relations and to formulate a prognostic index based on the most important prognostic variables.

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Patients and methods

During a one year period, 393 patients were consecutively admitted to the coronary care unit at Glostrup Hospital with acute myocardial infarction. Seventy six patients were excluded from the study: 48 in whom the symptoms of infarction had lasted for more than 15 hours before admission, 24 in whom a sufficient number of blood samples had not been obtained because the patient had died or been transferred to another department, and four who were admitted unconscious after cardiac arrest. Thus 317 patients were eligible for the study, of whom 43 died before the clinical evaluation and are not included in this report.

BLOOD SAMPLING AND ELECTROCARDIOGRAMS

Blood samples were drawn immediately after admission, and at 0800, 1400, and 2100 on the first three days, and at 0800 on the following four days. If pronounced pain recurred the frequent sampling procedure was repeated. Serum creatine kinase activity was measured according to the Scandinavian recommended method and serum creatine kinase isoenzyme activity by electrophoresis on agarose gel followed by fluorescence scanning.[13] The interassay variation of the creatine kinase isoenzyme MB activity is between 5% and 10% depending on the absolute value. An electrocardiogram in nine leads was recorded daily; changes indicating either transmural or subendocardial infarction were both considered to be positive. Infarct localisation was determined as anterior or inferior.

Every patient underwent electrocardiography during the entire hospital admission initially by Holter monitoring cable and later by telemetry. All were monitored with a sound track for time marking and for spoken comments, and all tapes were analysed daily by playback at increased speed with all abnormalities of the types mentioned below described and recorded on paper.

DEFINITION OF DIAGNOSIS

An acute myocardial infarction was defined as the occurrence of at least two of the following: (*a*) typical clinical symptoms, (*b*) typical electrocardiographic changes and (*c*) a temporary rise in serum creatine kinase isoenzyme MB activities above 30 U/l.[14] Congestive heart failure was diagnosed by the appearance on *x* ray film of cardiac enlargement or pulmonary congestion or both or by the presence of unequivocal clinical signs and symptoms. Cardiogenic shock was diagnosed when systolic blood pressure was persistently below 80 mm Hg, and the patient presented clinical signs of shock in the absence of any extracardiac cause. All the following cardiac arrhythmias were considered: ventricular extrasystoles, tachycardia and fibrillation, sinus arrest, supraventricular extrasystoles and tachycardia, second and third degree atrioventricular block, and asystole. Cardiac arrest was defined as ventricular fibrillation or asystole. The New York Heart Association functional class of symptoms of heart failure was estimated on day 7.

CALCULATION OF INFARCT SIZE

The estimation of infarct size by serum creatine kinase isoenzyme activity is based on the equation:

$$\text{Infarct size} = \int_0^T f(t)dt = k_d \cdot$$

$$\int_0^T E(t)dt + E(T) \approx k_d \cdot \int_0^T E(t)dt$$

E(t) is the specific creatine kinase isoenzyme MB activity (U/l) in serum at time t (hours). The function f(t) is the appearance function—that is, the hypothetical value for dE/dt without elimination. The factor k_d is the elimination constant (assuming first order kinetics). T is the time until creatine kinase isoenzyme MB activity can no longer be detected. We used the compartment as a model, which is described in detail elsewhere.[4]

FOLLOW UP

The patients were followed after discharge at intervals depending on late complications. Nevertheless, all survivors were given a full clinical examination one year after discharge. The time of death was ascertained as far as possible, either on readmission to hospital or by communication with the official registrar of persons and, when necessary, with relatives. The follow up was 100%.

STATISTICAL MODEL

The survival data were analysed by a regression model originally proposed by Cox.[15] The simplest formulation of Cox's model is as a model for the death rate λ(t), which uniquely determines the distribution of survival time. λ(t) can be thought of as the probability of dying on the t-th day, assuming that the patient survived the first t-l days. λ(t) is assumed to depend on certain prognostic factors (covariates) and to be as follows for a patient with covariates $z_1, \ldots\ldots, z_p$;

$$\lambda(t; z_1, \ldots, z_p) = \lambda_0(t) e^{\beta_1 z_1 + \ldots + \beta_p z_p}, \quad t > 0.$$

Here $\lambda_0(t)$, the underlying death rate, is an unknown and unspecified function of time. A consequence of the model is that death rates for any two patients are proportional—that is, the ratio between the death rates is not dependent on the time t.

If a covariate z_1 is defined to take the value 1 if some characteristic is present in the patient and 0 if it is not present (a qualitative covariate), but all other prognostic factors are equal, then the model assumes that the death rate at any time t after entrance for a patient with the characteristic is e^{β_i} times the death rate at t for a patient without it. If $\beta_i=0$ then the factor z_i has no influence on the death rate. Similar interpretation can be made for quantitative covariates such as age or estimated infarct size.

Estimates $\hat{\beta}_1,\ldots,\hat{\beta}_p$ of the regression coefficients were found by maximising the likelihood function of Cox.[15] Estimates of the survival function and the corresponding standard deviations were calculated for different values of the covariates according to Breslow[16] and Tsiatis.[17] In this analysis it can be determined by the graphical and numerical techniques by Andersen[18] whether the effects of various covariates can be described adequately by proportionality factors as mentioned above, and whether they enter the linear way, which the model assumes.

Not all the prognostic factors (Table 1) were available on the day of admission; for example, the estimate of infarct size was first available on the second or third day. The incidence of rhythm disturbances and cardiogenic shock was highest during the first days of admission. We chose to use the information available during the seven days after admission for practical reasons. By day 7 most of the serious complications had appeared, the clinical course has been determined, and the long term treatment plan had to be developed.

The evaluation of the variables was begun by using the 12 covariates shown in Table 1. The model was then reduced to a minimal set of covariates with a significant influence on the prognosis—that is the covariates from the set originally considered which did not contribute significantly to the prognosis were eliminated. Furthermore, we checked by a graphical technique[18] whether the effect of the covariates could be described by proportionality factors and whether they entered in a linear fashion. In cases where this was not so, the covariates were transformed accordingly. A prognostic index was defined as: prognostic index (PI): $\hat{\beta}_1z_1+\ldots..+\hat{\beta}_5z_5$, where $z_1,\ldots.,z_5$ are the covariates in the minimal set.

Results

Forty of the 274 (15%) patients who were alive on the seventh day died within the first year. Table 2 shows the prognostic variables which were significantly related to the one year survival: number of previous infarcts, age, estimated infarct size, heart failure, and NYHA class. Inclusion of other variables did not contribute significantly to the estimated prognosis. Graphical analysis showed that age and estimated infarct size had to be transformed to fit the model, and that NYHA class should enter as a bivariate (NYHA 1 or >1). Table 3 shows the estimates of the regression coefficients $\hat{\beta}_i$, estimates of the standard deviations for these, the statistic $\hat{\beta}_i$,/SD $(\hat{\beta}_i)$ and the corresponding p values. $\hat{\beta}_i$/SD $(\hat{\beta}_i)$ is an approximate standard normal deviate when $\beta_i=0$, so that it yields a test for the hypothesis that one of the covariates in the model is without effect, assuming that the other covariates are still taken into account. Heart failure and creatine kinase isoenzyme estimated infarct size were the prognostic variables most strongly related to mortality.

To illustrate the prognostic value of the estimated infarct size, the estimated survival function for two values of estimated infarct size are shown in Fig. 1. The estimated infarct sizes were 200 U/l (≃10 g) and 2000 U/l (≃120 g), and the other four significantly important prognostic variables were equal. The one year probability of survival was 0·87 and 0·69 respectively.

Figures 2 and 3 show the probability of survival as a function of time; (*a* and (*b*) compare the effects of the qualitative variable on the probability of survival. The effects of the quantitative variable (age and estimated infarct size) are compared by considering Fig. 2a against 2b and Fig. 3a against 3b respectively. For the different ages and estimated infarct sizes illustrated, the presence of heart failure was the most important single prognostic variable followed by NYHA class

Table 1 *Prognostic variables*

Variable	*Time evaluated*
Hypertension	Before admission
No of previous infarcts	Before admission
Age	On admission
Sex	On admission
Infarct localisation (ECG)	Days 1–3
Estimated infarct size (creatine kinase isoenzyme activity)	Davs 2–3
Heart failure	Days 1–7
Pulmonary oedema	Days 1–7
Cardiogenic shock	Days 1–7
Cardiac arrhythmias	Days 1–7
Cardiac arrest	Days 1–7
NYHA class	Days 1–7

Table 2 *Prognostic variables of significant importance for the one year survival according to the formula:*

$$\lambda(t;\, z_1,\ldots,z_5)=\lambda_0(t)e^{\beta_1z_1+\beta_2z_2+\beta_3z_3+\beta_4z_4+\beta_5z_5}$$

$z_1=\log_e$ (age 20 years)

$z_2=\begin{cases} 0 \text{ if NYHA class is } 1 \\ 1 \text{ if NYHA class is } >1 \end{cases}$

$z_3=$No of previous infarcts

$z_4=\begin{cases} 0 \text{ if heart failure is absent} \\ 1 \text{ if heart failure is present} \end{cases}$

$z_5=\log_e$ (estimated infarct size)

Table 3 *Estimates of regressions coefficients ($\hat{\beta}_i$), standard deviations (SD), and p values for the five prognostic variables of significant importance for the one year survival*

Prognostic variable	$\hat{\beta}_i$	$SD(\hat{\beta}_i)$	$\frac{\hat{\beta}_i}{SD(\hat{\beta}_1)}$	*p*
Age ($z_1 = \log_e$ (age—20))	1·67	0·73	2·29*	0·022
NYHA class (z_2)	1·04	0·42	2·50*	0·013
No of previous infarcts (z_3)	0·51	0·21	2·42*	0·015
Heart failure (z_4)	1·48	0·45	3·26*	0·001
Estimated infarct size ($z_5 = \log_e$ estimated infarct size)	0·41	0·16	2·60*	0·009

* $\frac{\hat{\beta}_i}{SD(\hat{\beta}_i)}$ is an approximate standard normal deviate when $\beta_i = 0$.

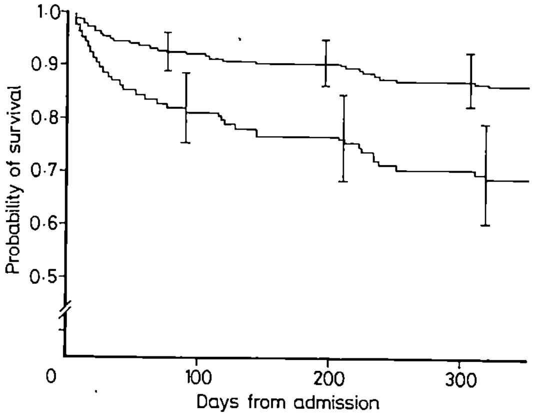

Fig. 1 *Probability of survival at least t days after the seventh day after admission, assuming that the patient was alive on day 7, for two patients aged 55 years old, in NYHA class >1, with no previous infarcts, and no heart failure. The patient indicated by the upper line had an estimated infarct size of 200 U/l, the other (lower line) one of 2000 U/l. Bars represent 1 SD.*

>1 and the presence of previous infarcts. The clinical importance of large infarct size or older age changes rapidly with the presence of other prognostic variables.

Figure 4 shows the relation between creatine kinase isoenzyme MB estimated infarct size and the probability of one year survival. The upper function represents a low risk combination of the other prognostic variables, the lower function a high risk combination. In patients without other poor prognostic variables the overall prognosis is good, and the clinical importance of the estimated infarct size is small. In the presence of other poor prognostic variables the probability of survival deteriorates rapidly as a function of infarct size. The difference in probability of one year survival between patients at low and high risk ranges between 8% and 35% depending on the estimated infarct size.

Figure 5 summarises the results of the analyses and shows the relation between the prognostic index (PI) and the probability of one year survival. The presence of few risk factors—that is, PI<10–11—indicates a very high probability of one year survival. A prognostic index above this level indicates a rapidly deteriorating one year prognosis.

Discussion

Recently estimated infarct size has been shown to be a prognostic variable which significantly influences the short as well as long term prognosis after acute myocardial infarction.[10 12] The aims of the present study were to quantify the relation between creatine kinase isoenzyme MB estimated infarct size and mortality and to determine its clinical importance in relation to other prognostic variables.

Two types of studies have been performed to evaluate the relation between serum enzyme estimated infarct size and mortality. Most studies have found an increased mean peak enzyme value or high estimated infarct size in those who died compared with survivors.[9 19 20]

These studies, however, provide no information on the prediction of the probability of mortality. Two studies have shown that in patients stratified according to creatine kinase or creatine kinase isoenzyme MB estimated infarct size, there is a significant prospective relation between estimated infarct size and mortality.[10 12] Nevertheless, neither the strength of the relation as a function of infarct size nor the influence on the relation of other prognostic variables have been determined.

The present study confirms that the creatine kinase isoenzyme MB estimated infarct size is a significant prognostic variable for mortality (Table 3). As shown previously, the mortality is highest during the first months after infarction (Fig. 1).[10 12] The influence of infarct size on the probability of one year survival is, however, dependent on the other prognostic variables (Fig. 2). In the absence of the other variables negatively influencing prognosis, the estimated infarct size has little influence on the probability of one year survival (Fig. 3). In the presence of these other prognostic variables the probability of one year survival is more influenced by infarct size (Fig. 4).

The 12 covariates estimated in the present study have previously been shown to be related to mortality after infarction.[21] Use of the Cox model of multivariate analysis provides the means of determining which of the covariates do not contain further information in the presence of the others. Of the covariates shown to be significantly related to mortality—infarct size, heart failure, NYHA class, number of previous infarcts, and age—only the creatine kinase isoenzyme MB estimated infarct size is not universally available in patients with myocardial infarction. Nevertheless, the estimate is easily calculated from serum samples drawn three times daily.[22]*

A few previous studies have compared creatine kinase estimated infarct size with other prognostic variables after infarction. Geltman *et al* showed that

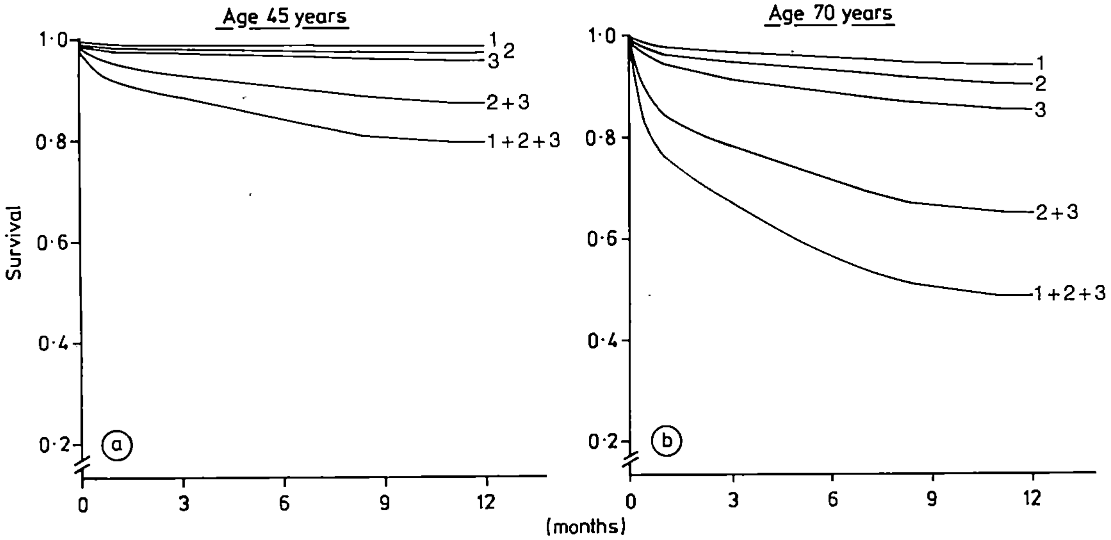

Fig. 2 *Probability of survival as a function of time for patients with different combinations of the prognostic variables. For the quantitative variables relevant constants were chosen: estimated infarct size 692 U/l (median value in the study population); age 45 and 70 years. The qualitative prognostic variables were: 1, presence of previous infarct; 2, NYHA class >1; 3, presence of heart failure.*

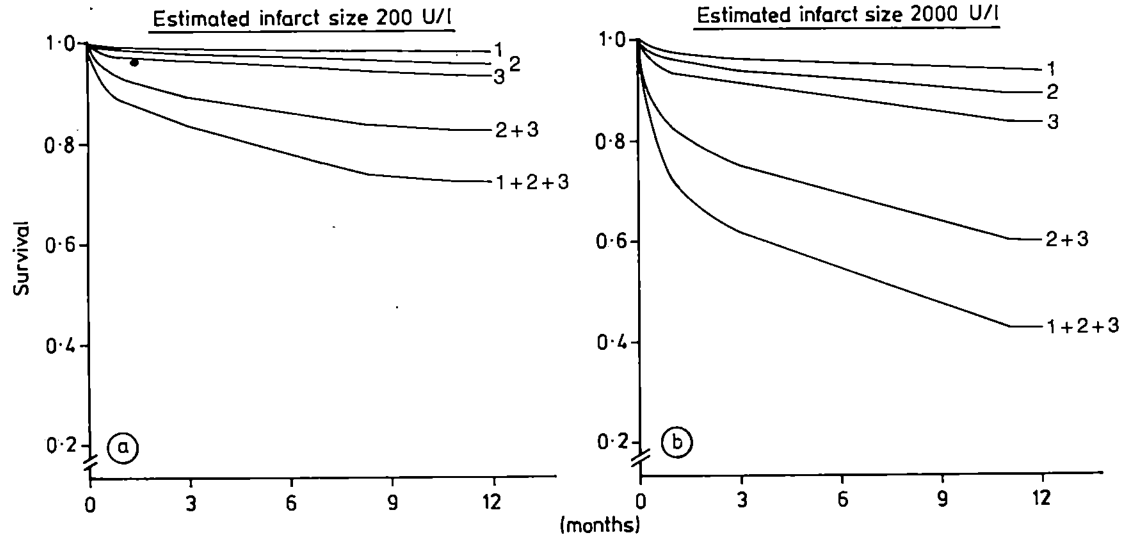

Fig. 3 *Probability of survival as a function of time for patients with different combinations of the prognostic variables. For the quantitative variables relevant constants were chosen: age 62 years (mean of the study population); estimated infarct size 200 U/l and 2000 U/l. The qualitative prognostic variables were: 1, presence of previous infarct; 2, NYHA class >1; 3, presence of heart failure.*

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*A full description of the estimation of infarct size is available on request.

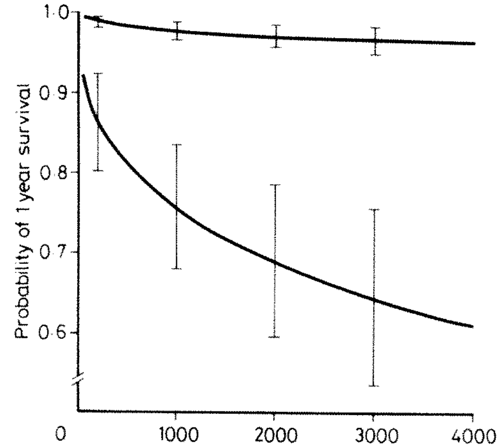

Fig. 4 *Probability of one year survival as a function of estimated infarct size. The functions represent the following combination of prognostic variables; the patient indicated by the upper line was aged 55 years, had no previous infarct, was in NYHA class 1, had no heart failure; the patient indicated by the lower line was aged 55 years, had no previous infarct, was in NYHA class >1, had heart failure. Bars represent 1 SD. CK-MB, creatine kinase isoenzyme.*

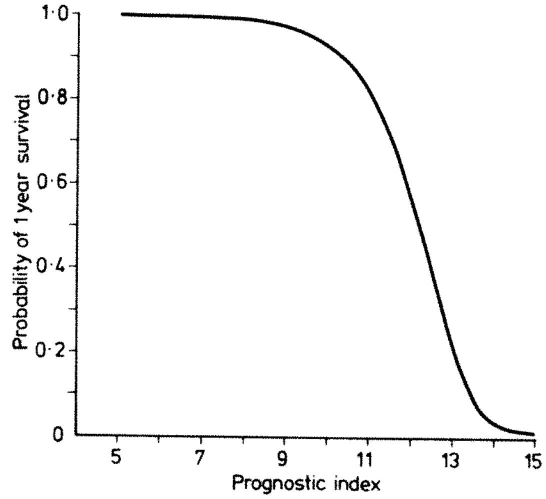

Fig. 5 *Relation between prognostic index* ($\hat{\beta}_1 z_1 + \ldots\ldots + \hat{\beta}_5 z_5$) *and probability of one year survival (see text).*

creatine kinase estimated infarct size and heart failure were the two variables most significantly associated with mortality after infarction.[10] Henning *et al* found creatine kinase estimated infarct size to be significantly related to mortality, and the estimate was included in a multivariate index together with several other variables to predict the mortality.[23] Nevertheless, total serum creatine kinase activity may be influenced by many clinical conditions and procedures, and the correlation between serum creatine kinase estimated infarct size and infarct size measured at necropsy is relatively low (r=0·63, SEE=42%).[4] In the present study, however, infarct size was estimated by a method based on measurements of the heart specific enzyme creatine kinase isoenzyme MB. This method has proved to be reliable for estimating infarct size in man, which is closely related to the extent of necrosis measured at necropsy (r=0·85, SEE=25%).[4]

The use of creatine kinase isoenzyme MB estimation provides an inexpensive, readily available non-invasive method for estimating infarct size. This method might be of primary importance for two main clinical reasons. Firstly, it may be useful as an endpoint in clinical trials aimed at limiting the extent of myocardial damage during myocardial infarction. Secondly, the clinician might use the estimated infarct size to determine the prognosis after infarction. The main purpose, however, of assessing the prognosis is to be able to improve treatment of the diseased patient. Thus, although a reliably estimated infarct size seems to be valuable for determining the prognosis, further clinical trials are needed to show if treatment based on the estimated infarct size improves the prognosis after an infarction.

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Prognostic significance of left ventricular ejection fraction after acute myocardial infarction
A bedside radionuclide study

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SUMMARY The prognostic significance of left ventricular ejection fraction measurements obtained at the bedside was assessed in 171 patients as soon as possible after acute myocardial infarction. Ejection fraction was measured with a radionuclide first pass portable probe method within a mean of 24 hours of the onset of major symptoms. The results were related prospectively to the subsequent incidence of ventricular fibrillation in hospital, and to hospital and postdischarge deaths in a mean follow up period of 15 (range 9–21) months. All eight episodes of primary ventricular fibrillation, all 12 deaths due to pump failure in hospital, and also 12 out of 13 postdischarge deaths occurred in that minority of 81 patients whose initial postinfarction left ventricular ejection fraction was <0·35. Multivariate correlation with clinical, enzymatic, and electrocardiographic indicators of myocardial infarction showed that the prognostic significance of these indicators could largely be explained by their association with low left ventricular ejection fractions. Left ventricular ejection fraction measured within the initial 24 hours after acute myocardial infarction predicts prognosis throughout the subsequent year.

Clinical studies have found that the prognosis after acute myocardial infarction depends mainly on the severity of clinical manifestations of left ventricular damage and dysfunction at the time of hospital admission.[1–3] Direct angiographic measurements of left ventricular function in patients with ischaemic heart disease who are being investigated for possible coronary artery bypass surgery have shown that left ventricular ejection fraction measurements are of major prognostic importance.[4 5] Nevertheless, the invasive nature of such measurements limits their application in patients with acute myocardial infarction. Minimally invasive first pass or equilibrium radionuclide methods for measuring ejection fraction directly from the relative decrease in left ventricular counts during systole[6] correlate well with contrast angiography and are well suited to studies in such patients. Their relative independence of geometric assumptions concerning left ventricular shape makes them more desirable for studies in patients with acute myocardial infarction than other non-invasive techniques.[7] The clinical application of such methods in this situation has therefore been advocated.[8] Nevertheless, whether or not the expense of such measurements might be justified by their independent clinical and prognostic significance has not yet been determined.

We, therefore, carried out this study to define the prognostic significance of abnormal left ventricular ejection fractions at admission to a coronary care unit after acute myocardial infarction.

Patients and methods

During the 12 month study period all patients admitted to the coronary care unit with a diagnosis of suspected acute myocardial infarction within the preceding 72 hours were invited to enter the study. A bedside radionuclide measurement of left ventricular ejection fraction was then performed as soon as possible, after informed consent had been obtained.

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Acute myocardial infarction was diagnosed when any two of the following were present: *(a)* a typical clinical history of acute myocardial infarction, *(b)* evolving electrocardiographic changes of acute Q wave or non-Q wave myocardial infarction, and *(c)* typical serum cardiac enzyme pattern of acute myocardial infarction based on creatine phosphokinase, serum aspartate aminotransferase, and lactate dehydrogenase activities; creatine phosphokinase isoenzymes were used when intramuscular injections had been given. In addition, postmortem confirmation of acute myocardial infarction was accepted.

This study included 171 patients with confirmed acute myocardial infarction (mean age 60 (9) (range 29–79) years), of whom 123 (72%) were male. These patients represented 91% of 188 patients with acute myocardial infarction admitted during the study period. The remaining 17 patients with acute myocardial infarction during this period were not studied either because of death within several hours of admission before study could be arranged (seven patients), inadequate venous access (four), an uninterpretable chest radiograph because of chest deformity (two), equipment malfunction (two), or consent withheld (two).

Left ventricular ejection fraction results in 15 patients admitted to hospital in whom no clinical, electrocardiographic, or radiological evidence of heart disease was found were used as a control group. In all of these patients a non-cardiac diagnosis for their symptoms was made, and no symptoms or signs of heart disease developed in the following 12 months.

RADIONUCLIDE TECHNIQUE

All ejection fraction measurements were made at the bedside using the portable probe initial transit method described by Steele *et al.*[9] Results obtained with this method have been found to correlate well with contrast left ventriculography by three groups of workers.[9-11]

The portable probe detector was positioned perpendicular to the chest wall over the heart and the left ventricular position ascertained as follows. A metal paper clip was taped to the patient's precordium in the fourth or fifth left intercostal space, 4–6 cm from the mid-sternal line. A chest radiograph was then taken with the patient supine and breathing quietly. This radiograph was used to determine the chest wall surface point overlying a point halfway between the midline and the cardiac apex and halfway between the upper and lower borders of the heart shadow. A circular cardboard target was taped to the precordium with its central hole over the point thus defined as overlying the mid left ventricle. Patients were studied supine or with their trunk tilted upright by 15°–30° if the supine position caused dyspnoea.

The radionuclide used was either ionic indium-113m 1–2 mCi (37–74 MBq), which binds to plasma transferrin to become an intravascular marker, or 1–2 mCi (37–74 MBq) of technetium-99m labelled human serum albumin. Each radionuclide dose was prepared in a volume of 1·0 ml and administered as a compact bolus using 5 ml of saline flush. All radionuclide injections were given through a 61 cm antecubital intravenous line whose tip was in the superior vena cava.

Two bolus injections of radionuclide were given 5–10 minutes apart for each study, the first for assessment of raw left ventricular activity, the second for the assessment of "background". The initial transit of each bolus though the heart was detected with a collimated sodium iodine scintillation probe (Phillips). Lead collimation was used according to the specifications of Steele[9] and centred precisely on the precordial target. For recording raw left ventricular activity annular lead shielding with a circular central portal 5 cm in diameter was used. For recording background activity, a 5 cm diameter lead disc was centred over the left ventricle, and activity in an annular region around this lead disc was recorded.[9]

Resultant activity was recorded with a high quality x–y plotter (Hewlett-Packard). A ratemeter time constant of 0·10 s was used for slow heart rates (<70 beats/min) to minimise statistical noise, whereas a time constant of 0·05 s was used for higher heart rates to avoid overdamping of the activity-time curves. The resultant left ventricular and background activity curves were recorded on transparent graph paper. The curves were superimposed and matched at two points: *(a)*, the initial upwards deflection and *(b)* the horizontal tail after the initial transit was complete (Fig. 1). This matching was made more reproducible and simple by choosing the dose for the second (background) injection so that the tails of the two curves would have the same vertical height.[12] In practice this meant using from 30% to 50% as much activity for the second (background) bolus as for the first. The pulmonary transit time (Fig. 1) was measured from the time when the right ventricular peak had fallen to 75% of its peak level to the time of peak left ventricular activity, as recommended by Pierson and Van Dyke.[13]

Calculation of ejection fraction—Left ventricular ejection fraction was measured from the fractional decrease in net ventricular activity for each cardiac cycle, from the time of peak left ventricular activity until just before recirculation became apparent on either of the time-activity curves. The mean value of these individual cardiac cycles was used (Fig. 2).

Reproducibility of the method—Duplicate studies within half an hour in 35 patients showed highly reproducible results for ejection fraction: (initial

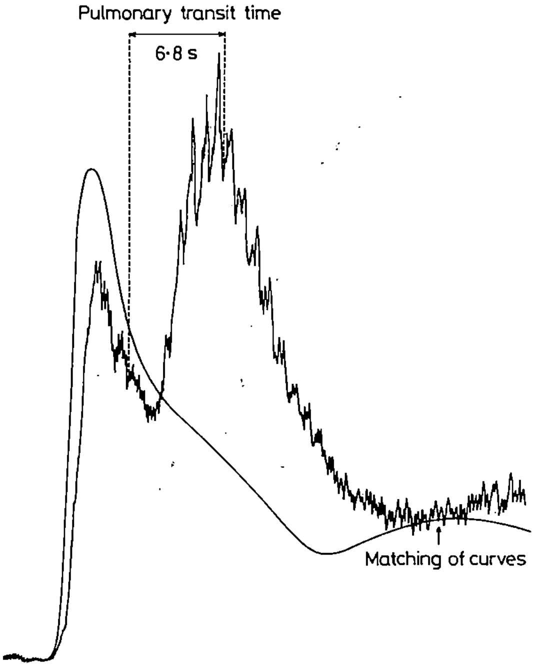

Fig. 1 *Left ventricular time-activity curve (showing systolic to diastolic fluctuations in activity) with superimposed background (smooth trace) time-activity curve. The first of the two large peaks on the ventricular curve is due to right ventricular transit, whereas the taller second main peak is due to left ventricular bolus transit.*

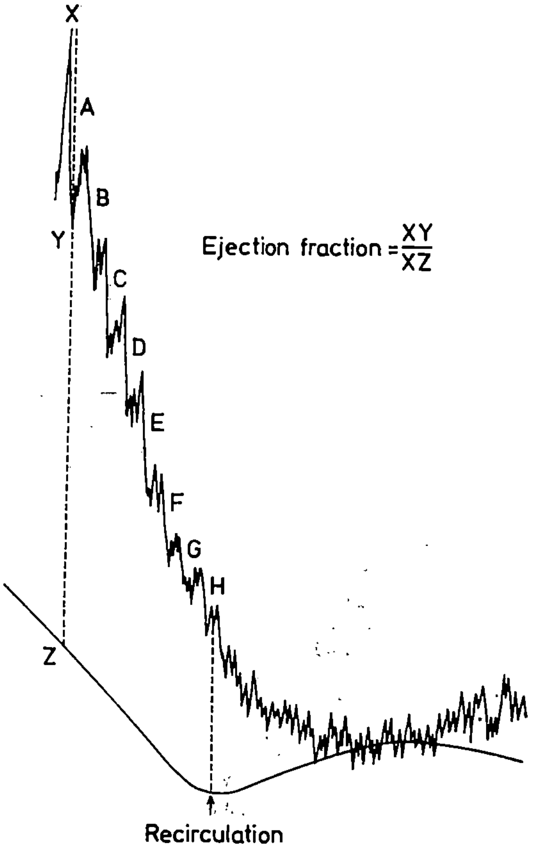

Fig. 2 *Method of calculating left ventricular ejection fraction from the beat to beat fluctuations in net left ventricular activity (that component above the superimposed and matched background curve.) X–Z, end diastolic counts; Y–Z, end systolic counts (mean taken over cardiac cycles A–H).*

study 0·41 (0·13), second study 0·41 (0·12) with a standard deviation between the paired results of 0·04, r=0·95). In a further 14 patients measurements were made sequentially within two hours with the portable probe method and with a first pass method using a gammacamera interfaced to a minicomputer. Data for the latter were acquired in dynamic format in the 45° left anterior oblique projection and analysed as described by Steele *et al.*[12] This gammacamera method was analogous to the probe method except that it enabled much more certain determination of left ventricular location. The ejection fraction results from these two radionuclide methods were not significantly different (probe 0·38 (0·14); gammacamera 0·36 (0·13) and correlated strongly with each other (r=0·95). This suggested that the procedure for placing the probe used in this study successfully minimised potential errors due to malpositioning over the precordium.

PROGNOSTIC ANALYSIS

The initial ejection fraction value obtained after infarction was exclusively used for prognostic analysis. The median delay between the onset of symptoms and recording the initial value was 23·5 (range 1–71) hours. Twenty two patients were studied twice, initially within the first 24 hours and again 24 hours later, to determine the validity of considering together the prognostic significance of ejection fraction measurements obtained more and less than 24 hours after the onset of symptoms. The initial ejection fraction was related to the incidence of defined endpoints in hospital and after discharge from hospital.

Inhospital follow-up—The mean duration of hospital admission was 8–12 days. The inhospital endpoints were defined as follows: (*a*) primary ventricular fibrillation—ventricular fibrillation occurring without preceding cardiogenic shock; (*b*) pump failure death—death in hospital in a state of intractable cardiogenic shock or pulmonary oedema without clinical or necropsy evidence of a mechanical cardiac defect such as rupture of the interventricular septum, papillary muscle, or free left ventricular wall; *(c)* other cardiac deaths—all cardiac deaths not due to pump failure as defined above.

Postdischarge follow up—The mean follow up period was 15 (range 9–21) months. The endpoints were defined as follows: *(a)* postdischarge sudden cardiac death—sudden death in the absence of clinical shock or cardiac failure with or without the onset of chest pain within the preceding hour; and *(b)* non-sudden cardiac death—death due to pump failure, which in all cases was associated with readmission to hospital.

STATISTICAL METHODS

Left ventricular ejection fractions are expressed as mean (standard deviation). Statistical analyses were performed with a Cyber 73 computer and the SPSS package of statistical programmes.[14] Differences in mean left ventricular ejection fraction between subgroups were assessed using analysis of variance. Cross tabulations of non-continuous variables were analysed for statistical significance using the χ^2 test. Comparison of the prognostic significance of ejection fraction and clinical variables was performed with discriminant function analysis.

Results

OVERALL EJECTION FRACTION RESULTS

The mean ejection fraction in the 171 patients with acute myocardial infarction was 0·36 (0·11) (range 0·12–0·62). The mean value in the 15 control subjects without heart disease was 0·62 (0·07) (range 0·50–0·76). Only 11% of the patients with acute myocardial infarction had an ejection fraction >0·50, the lowest level found in the 15 control subjects.

In the 22 patients who had measurements both within the first 24 hours after the onset of symptoms and again 24 hours later, mean left ventricular ejection fraction was 0·35 (0·10) at the initial measurement and 0·36 (0·11) 24 hours later (NS). Interstudy variability (standard deviation 0·04, r=0·92) was not significantly different from that obtained in the 35 patients who had two studies <30 minutes apart.

RELATION TO HISTORICAL, ENZYMATIC, AND ELECTROCARDIOGRAPHIC FINDINGS

Ejection fraction was not significantly related to sex, age, or history of angina. It was related to the number of previous myocardial infarctions (p<0·001); none, 0·38 (0·11) (n=125); one, 0·32 (0·10) (n=34); two, 0·24 (0·12) (n=9); more than two, 0·17 (0·7) (n=3). Ejection fraction was also related to enzymatic indices of the extent of acute myocardial necrosis (r=0·29 *v* peak creatine phosphokinase activity; p<0·001). The combination of peak creatine phosphokinase activity and the number of previous infarctions predicted ejection fraction better than either variable alone (multiple r=0·51; p<0·001 for each variable; Table 1).

Table 1 *Cumulative effect of peak creatine phosphokinase activity and history of previous myocardial infarct on severity of depression of left ventricular ejection fraction. Values are mean (SD) left ventriclar ejection fraction (numbers in parentheses are numbers of patients in each subgroup*)*

	Peak creatine phosphokinase activity (IU/l)		
	<1000	*1000–2500*	*>2500*
No previous infarct	0·40 (0·09) (74)	0·36 (0·09) (37)	0·26 (0·07) (6)
One or more previous infarcts	0·32 (0·10) (31)	0·26 (0·12) (10)	0·16 (0·14) (2)

*Eleven patients were not included because early death or resuscitation from ventricular fibrillation within the first 24 hours prevented estimation of peak creatine phosphokinase activity.

The electrocardiographic site of infarction was strongly (p<0·001) and the presence or absence of pathological Q waves was weakly (p<0·05) related to ejection fraction. Among the 154 patients whose infarct location could be determined from the electrocardiographic changes, mean ejection fraction was highest with inferior infarction (0·41 (13); n=76), lower with anterior infarction (0·34 (11); n=57), and lowest with combined anterior and inferior infarction (0·29 (13); n=21); even lower values were found when the site of infarction was obscured by the presence of left bundle branch block (0·24 (11); n=11). Mean ejection fraction was lower in patients with Q waves (0·34 (10); n=101) than in those without (0·38 (12); n=59) (p<0·05; left bundle branch block excluded). The additive nature (p<0·001) of the interrelations between the electrocardiographic findings, history of previous infarction, and ejection fraction is shown in Table 2.

Table 2 *Additive effect on left ventricular ejection fraction of history of previous myocardial infarction, site of electrocardiographic localisation, and presence of Q waves. Values are mean (SD) left ventricular ejection fractions (numbers in parentheses are numbers of patients in each subgroup*)*

	Site of infarct		
	Inferior	*Anterior*	*Anteroinferior or LBBB*
No Q wave, initial infarct	0·44 (0·08) (15)	0·39 (0·09) (14)	0·31 (0·11) (2)
Q wave, initial infarct	0·41 (0·07) (43)	0·32 (0·11) (35)	0·31 (0·10) (10)
No Q wave, recurrent infarct	0·39 (0·09) (7)	0·32 (0·10) (6)	0·31 (0·09) (6)
Q wave, recurrent infarct	0·32 (0·12) (11)	0·23 (0·04) (2)	0·23 (0·12) (14)

*Six patients without localising electrocardiographic features are not included. LBBB, left bundle branch block.

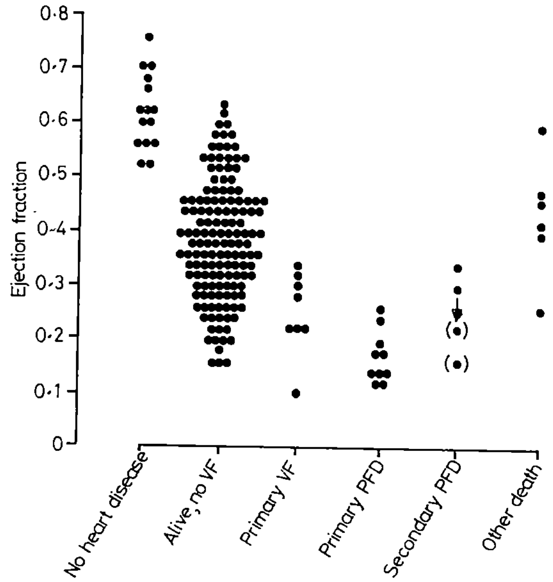

Fig. 3 *Individual admission ejection fractions for the 15 normal subjects and for status at hospital discharge of the 171 patients with acute myocardial infarction. VF, ventricular fibrillation; PFD, pump failure death; arrow indicates a fall in ejection fraction after reinfarction.*

INHOSPITAL PROGNOSIS

Fig. 3 shows the relation of admission ejection fraction to status at discharge. The 145 patients who left hospital alive without requiring resuscitation from ventricular fibrillation had a mean admission ejection fraction of 0·38 (0·11). The eight patients who had primary ventricular fibrillation in hospital had significantly lower admission ejection fractions (mean 0·24 (0·06), $p<0·001$); all left hospital alive after resuscitation.

In all 12 patients who died of pump failure initial ejection fraction after the fatal episode of infarction was $<0·35$. Ten patients who died from primary pump failure without clinical evidence of reinfarction had a mean admission ejection fraction of 0·18 (0·05). The two other patients to die of pump failure in hospital did so after reinfarction. The initial ejection fractions in these two patients were initially higher than in the other patients to die of pump failure (mean 0·32 (0·04) but fell when remeasured within 24 hours of reinfarction (mean 0·19 (0·05)) (Fig. 3). Individual ejection fractions in the group of patients who subsequently died of pump failure overlapped considerably with those of other subgroups (Fig. 3). There was much less overlap between the pulmonary transit times of the patients who died of pump failure (mean 17·6 (3·8) s, range 11–22 s) and those of other patients (mean 8·1 (3·4) s, range 4–29 s) (Fig. 4). Pulmonary transit time was >14 s in 11 out of 12 patients who died in hospital of pump failure but in only 3 out of 159 others ($p<0·001$).

In the six patients who died in hospital of cardiac causes other than pump failure the mean admission ejection fraction was 0·44 (0·11), which is not significantly different from the values found in the hospital survivors. The causes of death in this group of patients comprised cardiac rupture (two), electromechanical dissociation (one), and ruptured papillary muscle or ruptured interventricular septum (three). In these three patients the radionuclide time activity curves suggested a left to right shunt; in each case they differed from those of all other patients in showing a very prolonged washout phase of the left ventricular peak despite normal pulmonary transit times and an ejection fraction >0·35.

POSTDISCHARGE PROGNOSIS

Of the 153 hospital survivors, 13 (9%) died during follow up. Three of the deaths were due to cardiac failure, whereas 10 were sudden. Of the sudden deaths, fatal collapse was witnessed in six, but unwitnessed in two and was due to documented ventricular fibrillation after the onset of chest pain in the remaining two.

Fig. 5 shows the relation between admission ejection fractions and the follow up status of hospital survivors. The mean admission ejection fraction in the 13 patients who died after discharge was significantly lower (0·25 (0·09)) than in the 140 patients still alive a mean of 15 months after acute myocardial infarction (0·38 (0·10); $p<0·001$). In the 10 patients who died suddenly during follow up the mean ejection fraction was 0·27 (0·09), and in the three patients whose death was not sudden it was 0·19 (0·09) (NS *vs* sudden deaths). The patients who died during follow up included all three hospital survivors with pulmonary transit times >14 s (Fig. 4).

TOTAL EFFECT ON PROGNOSIS

Table 3 summarises the overall association between prognosis and admission ejection fraction; all episodes of primary ventricular fibrillation or of death due to pump failure in hospital and all but one postdischarge death occurred when the admission ejection fraction was $<0·35$.

PROGNOSTIC ACCURACY OF ADMISSION EJECTION FRACTION *vs* *CLINICAL INDICES*

Discriminant function analysis showed that the admission ejection fraction had greater overall prognostic significance for the development of ventricular fibrillation, pump failure death, or postdischarge death than any non-radionuclide variable. A history of previous infarction, peak creatine phosphokinase

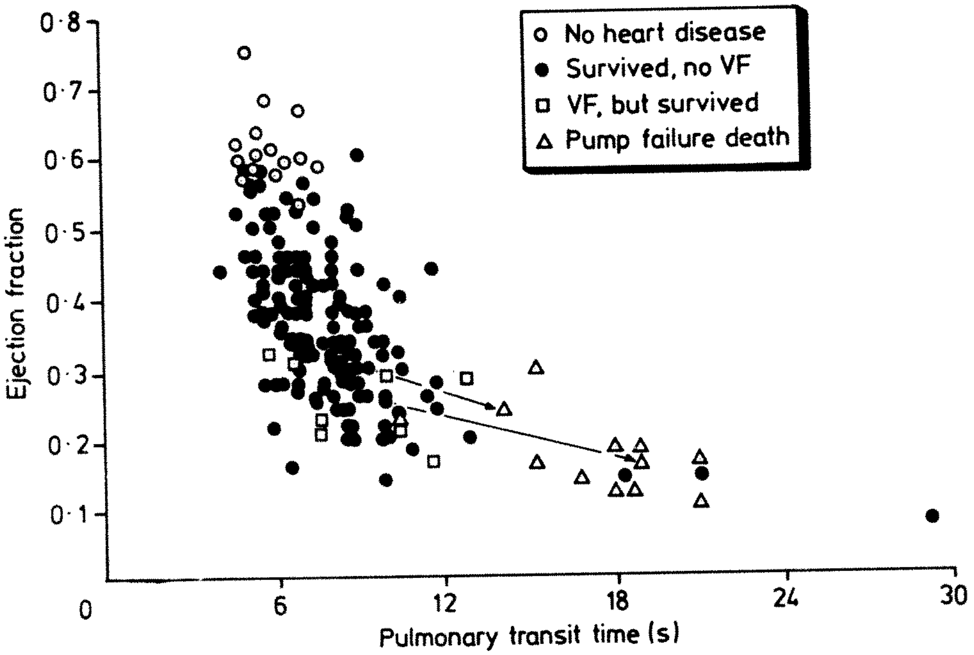

Fig. 4 *Ejection fraction in relation to pulmonary transit time, diagnosis, and inhospital prognosis. Patients who died of other causes than pump failure death are not shown. VF, primary ventricular fibrillation (arrows indicate changes with recurrent infarction).*

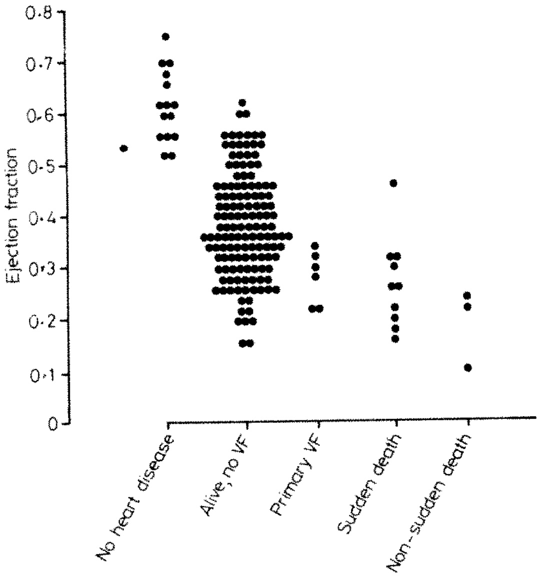

Fig. 5 *Individual admission ejection fractions of the normal subjects and the 153 hospital survivors of acute myocardial infarction in relation to status at the end of follow up after discharge. VF, ventricular fibrillation before hospital discharge.*

Table 3 *Overall relation of admission left ventricular ejection fractions to prognosis except for deaths attributable to mechanical cardiac defects*

	Ejection fraction	
	>0·34	*<0·35*
No of patients	90	81
(A) With primary ventricular fibrillation	0	8
No of deaths:		
(B) In hospital due to pump failure	0	12
(C) After discharge	1	12
No (%) of patients with (A), (B), or (C)	1 (1)	30† (36)*

*$p<0·001$.
†Two patients had both (A) and (C).

activity, and electrocardiographic features had no independent prognostic significance for these endpoints when the ejection fraction was known. The most prognostically important non-radionuclide variable was the appearance of the lung fields on the initial chest radiograph. Table 4 shows the interrelation between these prognostic endpoints, the chest *x* ray findings, and an ejection fraction <0·35. Both the ejection fraction and the chest *x* ray findings had independent prognostic significance, but that of the ejection fraction was greater.

P 25,728

Table 4 *Additive overall prognostic value of left ventricular ejection fraction and the appearance of the lungfields on the initial chest radiograph for ventricular fibrillation, death due to pump failure in hospital, and death after discharge. For each subgroup the number of patients with one or more of these prognostic end points/total patients in subgroup (%) is indicated.*

Lung fields	*Left ventricular ejection fraction (% of patients)*	
	>0·34	*<0·35*
Normal	1/75 (1)	10/48 (21)
Congested	0/9 (0)	5/10 (50)
Pulmonary oedema	0/6 (0)	15/23 (65)

Discussion

This study adds to previous evidence on the prognostic importance of left ventricular ejection fraction in patients with myocardial infarction. A strength of this study in comparison to other studies is the inclusion of a near complete spectrum of a large group of consecutive patients admitted with myocardial infarction to a coronary care unit over 12 months. In particular, the study protocol is unique in that it enabled left ventricular ejection fraction to be obtained in significant numbers of patients before ventricular fibrillation and before death due to pump failure. Other strengths of the study include the measurement of ejection fraction within 72 hours of the onset of symptoms in all cases and the correlation of results with both inhospital and postdischarge prognosis in relation to clinical variables. Our ejection fraction measurements were obtained with the first pass portable probe radioisotope method described by Steele *et al.*[9] This technique was able to obtain bedside data from these critically ill patients more promptly, more conveniently, and less expensively than radionuclide ventriculography with a portable gammacamera and computer.

The range of admission ejection fractions in this large group of patients after acute myocardial infarction (mean 0·36 SD 0·12) is similar to radionuclide results found in smaller groups by Rigo *et al*[15] and by Schelbert *et al.*[16] Our results suggest that there is little overall change in ejection fraction in the first 24–72 hours after myocardial infarction.

HOSPITAL PROGNOSIS

The correlation of admission ejection fractions with subsequent clinical outcome has confirmed and extended the finding by Rigo *et al*,[15] Schelbert *et al*,[16] and Shah *et al*[17] that ejection fractions <0·35 soon after acute myocardial infarction are related to hospital mortality, primarily from pump failure. Nevertheless, ejection fractions in patients who died in hospital of pump failure still appreciably overlapped those of other groups of patients, and a better prediction of death due to pump failure by pulmonary transit times was possible. Prolongation of pulmonary transit time probably adds independently important prognostic information when ejection fraction is severely depressed. Presumably this is because it reflects both decreased cardiac output and also to a lesser extent increased lung blood volume. There may, however, be inaccuracies in measuring very low ejection fractions; non-gated radionuclide techniques tend to overestimate very low ejection fractions and cannot resolve decreases in ejection fractions <0·15–0·20 owing to Poisson statistical fluctuation in recorded counts.[18] Although these statistical uncertainties are less with a probe detector[9–11] than a gammacamera, this factor could still have prevented accurate resolution of ejection fractions <0·15 in this study.

Schulze *et al*[19] reported that high grade ventricular arrhythmias detected with 24 hour ambulatory electrocardiograms before discharge after acute myocardial infarction were virtually confined to that subgroup of patients whose predischarge radionuclide ejection fraction was <0·40. Our study has further shown that ejection fractions in this range are highly related to the risk of ventricular fibrillation in hospital, as all such episodes occurred in patients with admission ejection fractions <0·35.

In contrast to death due to pump failure and potential death due to ventricular fibrillation, death due to cardiac rupture and other mechanical defects could not be predicted by ejection fraction in our study.

POSTDISCHARGE PROGNOSIS

As with pump failure death or ventricular fibrillation in hospital, mortality in the postdischarge follow up period occurred mainly in patients whose admission ejection fraction was <0·35, with 12 out of 13 postdischarge deaths occurring in this subgroup. These findings of the postdischarge phase of our study agree with those of other studies which obtained radionuclide ejection fraction measurements under resting conditions at a later period after myocardial infarction, shortly before discharge from hospital.[20 21] They also agree with combined rest and exercise left ventricular ejection fraction studies after recovery from acute myocardial infarction,[22 23] which have found that ejection fraction <0·35 at rest was the major independent predictor of death in the subsequent year. Thus our results indicate that ejection fractions measured immediately after hospital admission have as much prognostic value after discharge as those measured immediately before, or shortly after, discharge from hospital.

EJECTION FRACTION, VENTRICULAR FIBRILLATION, AND SUDDEN DEATH

In this study nine out of 10 postdischarge sudden deaths occurred in patients with ejection fractions $<0\cdot35$. A strong association between ejection fractions $<0\cdot35$ measured two weeks after infarction and sudden death in the following year has been reported by Schulze *et al.*[24] Sudden cardiac deaths are most likely to be due to ventricular fibrillation, and in two of the postdischarge sudden deaths this was directly documented. Furthermore, all eight of our patients who had primary ventricular fibrillation in hospital had admission ejection fractions $<0\cdot35$. Our study therefore shows evidence of a pronounced association between advanced left ventricular dysfunction after acute myocardial infarction and susceptibility to ventricular fibrillation. In contrast to ejection fractions, ventricular arrhythmias detected during monitoring in the coronary care unit were not significantly predictive of either ventricular fibrillation in hospital or sudden death after discharge. Braat *et al*[25] have recently reported that ejection fractions $<0\cdot40$ strongly predicted sustained ventricular tachycardia during six weeks of continuous ambulatory electrocardiographic monitoring but that the presence or grade of ventricular arrhythmias detected on 24 hour ambulatory electrocardiograms after acute myocardial infarction did not. Our data add to those of Schulze *et al*[24] and Braat *et al*[25] on the importance of the association between low ejection fractions and fatal ventricular arrhythmias, specifically with regard to documented ventricular fibrillation. Presumably this association is related to the amount of unstable ischaemic myocardium which is present when the ejection fraction is $<0\cdot35$.

PROGNOSTIC SIGNIFICANCE OF EJECTION FRACTION RELATIVE TO CLINICAL VARIABLES

The additive ability of the number of previous infarctions, peak cardiac enzyme activity, and electrocardiographic indicators of site and severity of myocardial infarction to predict ejection suggests that ejection fractions reflect the cumulative extent of left ventricular damage from both present and previous infarcts. The fact that these non-radionuclide variables had no independent prognostic significance when ejection fraction results were known suggests that their pronostic significance is primarily attributable to their association with depressed left ventricular ejection fractions.

The potential clinical value of ejection fraction measurements after myocardial infarction depends largely on whether their prognostic significance adds to that of more easily obtained clinical information. Our discriminant function analysis results indicate that ejection fraction measurements do add to the prognostic data obtainable from standard clinical, enzymatic, electrocardiographic and radiographic investigations.

This study was supported by a grant from the National Heart Foundation of Australia.

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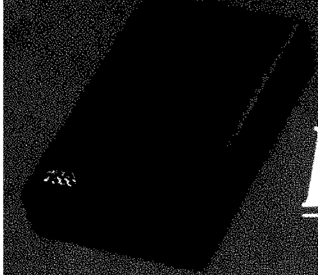

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Sharpe D N, Coxon R, Am Heart J 1982; 104: 1164-1171.

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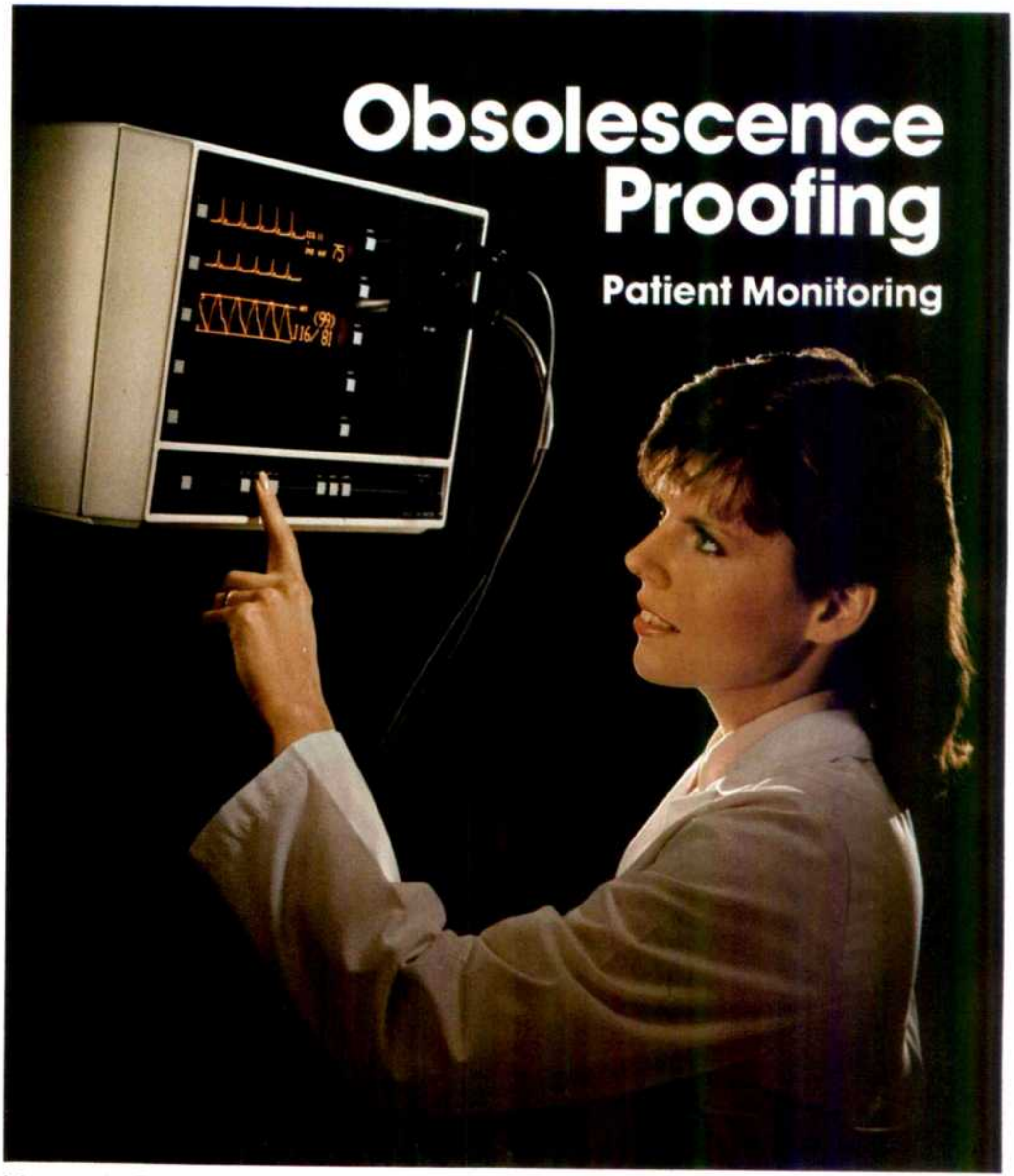

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Br Heart J 1985; 53: 25–9

Myocarditis confirmed by biopsy presenting as acute myocardial infarction

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SUMMARY Two cases of acute myocardial infarction occurred in association with myocarditis, which was confirmed by biopsy. The first patient suffered an anteroseptal and the second patient an inferior wall myocardial infarction shortly after an acute viral illness. In both patients, coronary angiography showed normal coronary arteries, and right ventricular endomyocardial biopsy confirmed myocarditis. Histological abnormalities attributable to ischaemic heart disease were absent. The first patient's condition became stable after immunosuppressive treatment. Myocarditis resolved spontaneously within three months in the second patient. Coronary artery spasm and myocardial involvement with a systemic disease were unlikely.

Endomyocardial biopsy in patients with acute myocardial infarction and normal coronary arteries may be useful in identifying myocarditis associated with myocardial necrosis. Myocarditis in acute myocardial infarction in the absence of coronary artery obstruction has not previously been documented during life.

Systemic viral infection is often complicated by acute myocarditis in man, but the actual pathophysiology of the resulting myocardial dysfunction is unclear.[1] Animal models of enteroviral myocarditis have elucidated the pathogenesis of human myocardial inflammation.[2] Murine Coxsackie virus B1 and B4 infection produce not only extensive myocardial inflammation but also coronary arteritis,[3] localised myocardial necrosis, and, occasionally, ventricular aneurysms, indistinguishable from those following myocardial infarction induced by epicardial coronary artery obstruction.[4 5] The presence of myocarditis in patients who suffered myocardial infarction despite the absence of coronary artery disease has been found at necropsy.[6] The occurrence of myocarditis in this setting has not been previously documented during life, and a causal relation between the two entities remains controversial. It is estimated that 1% of all myocardial infarctions[7] and up to 17% of myocardial infarctions occurring in younger patients occur without demonstrable coronary artery disease.[8] We report two cases of myocardial infarction occurring in association with myocarditis confirmed by biopsy.

Patients and methods

CASE REPORTS

Case 1

A 56 year old man had long standing rheumatoid arthritis, without extra-articular manifestations, which was chronically treated with low dose corticosteroids. Shortly after a viral syndrome with high fever, sore throat, myalgias, and anorexia he developed severe pressure-like substernal chest pain radiating to the left jaw and lasting several hours. Serial electrocardiograms showed the evolution of extensive anterolateral injury and an old inferior wall myocardial infarction. Cardiac catheterisation, performed two weeks after the acute event, showed a large apical aneurysm with filling defects suggestive of mural thrombi. The coronary arteries were essentially normal. Four months later, in view of persisting symptomatic congestive heart failure, he was referred to determine possible myocarditis.

On physical examination his blood pressure was

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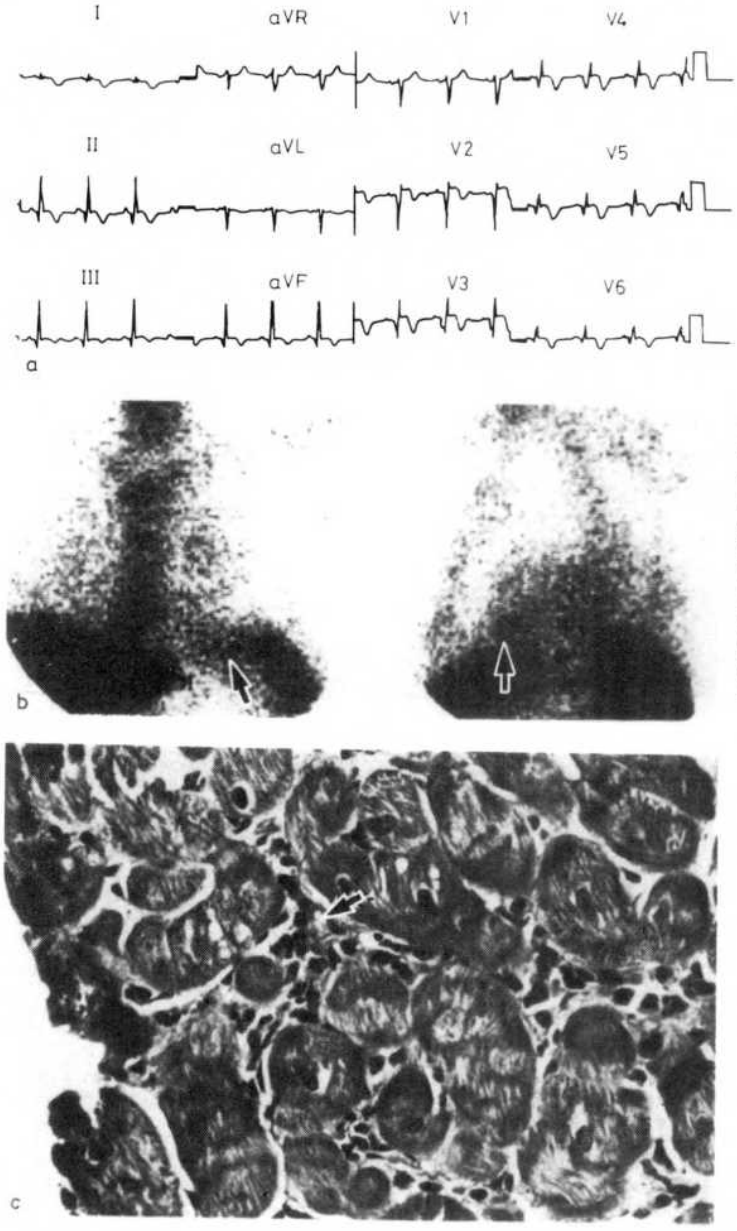

Fig. 1 *Case 1: (a) electrocardiogram showing extensive anterolateral infarction with ST elevation in leads V2–V6 and an old inferior wall myocardial infarction. (b) A gallium^{67} scan in the anterior and 45° left anterior oblique projection showing myocardial uptake (arrows). (c) Photomicrograph of endomyocardial biopsy specimen showing interstitial lymphomononuclear cell infiltration (arrow) and myocyte necrosis (haematoxylin and eosin, original magnification × 200).*

114/78 mm Hg, pulse rate 88 beats/min, respiration rate 24/min, and temperature 36·8°C. Cardiac examination showed a diffuse apical impulse with a summation gallop. Rales were heard in both lung bases, and pedal oedema was present. An electrocardiogram showed the residual changes of an extensive anterolateral infarction with persistent ST elevation in V2–V6 as well as the old inferior wall myocardial infarction (Fig. 1a). His initial laboratory tests showed a normal differential blood count, serum protein electrophoresis, and concentration of complement. The rheumatoid factor was positive at a titre of 1/1280. Antinuclear factor was absent. Coxsackie B1–B6 serum antibody titres were $<1/8$. A chest radiograph showed mild cardiomegaly. Autologous indium^{111} leucocyte and gallium^{67} scans showed pronounced myocardial uptake (Fig. 1b). Radionuclide ejection fraction was 17% with the apical aneurysm.

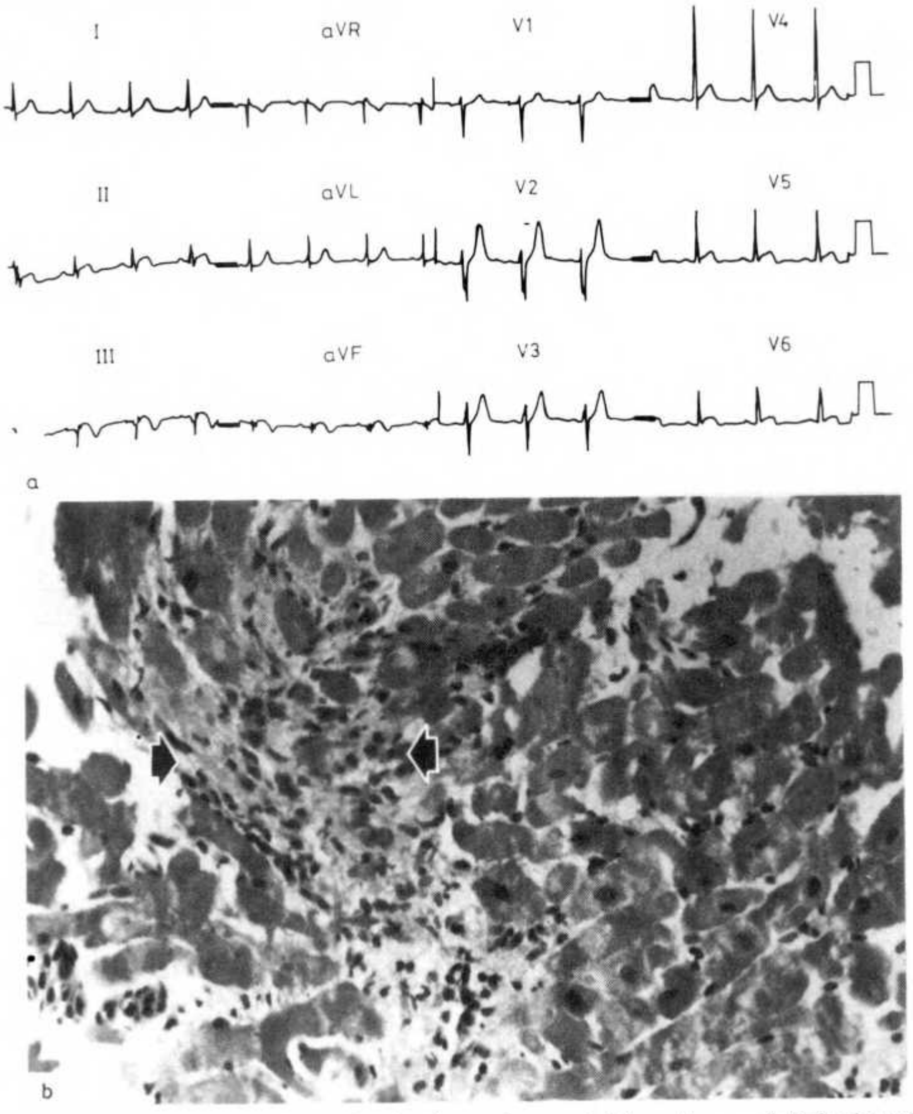

Fig. 2 *Case 2: (a) electrocardiogram showing changes of an acute inferior wall myocardial infarction and (b) photomicrograph of endomyocardial biopsy specimen showing lymphomononuclear infiltration, myocyte necrosis, and fibrosis (arrows) (haematoxylin and eosin, original magnification × 100).*

A right ventricular endomyocardial biopsy showed focal perivascular and myocardial lymphocytic infiltration with myocyte necrosis, consistent with active myocarditis. No interstitial oedema, polymorphonuclear leucocyte infiltration, or coagulation necrosis of the myocytes was seen (Fig. 1c).

Immunofluorescence showed no immunoglobulin or complement deposition in the heart. Viral cultures and electron microscopy failed to demonstrate virus in the myocardium. The prednisone dosage was increased and azathioprine was added. The patient's condition was stable 16 months after the event.

Case 2

A 17 year old previously healthy white boy presented with a one week history of sore throat, low grade fever, sporadic daily palpitation, and pressure-like non-pleuritic chest pain radiating to his left shoulder. On physical examination his blood pressure was 110/68 mm Hg, heart rate 71 beats/min, respiration rate regular at 16/min, and temperature 38·2°C. The throat was erythematous. Cardiac examination showed a normal apical impulse and heart sounds, a flow murmur, and physiological third heart sound. He had no pericardial friction rub or hepatosplenomegaly.

A telemetry rhythm strip obtained on admission showed a short episode of accelerated idioventricular rhythm. Laboratory values showed a mild leucocytosis with left shift, an erythrocyte sedimentation rate of 56 mm in the first hour, and negative blood and throat cultures. Ebstein-Barr and Coxsackie viral titres, and antistreptolysin O titre were within normal range. His peak creatinine phosphokinase activity was 857 IU/l with a strongly positive MB band, serum aspartate aminotransferase activity 150 IU/l, and lactate dehydrogenase activity 558 IU/l. His cardiac enzyme values gradually returned to normal over three days showing the classic evolutionary pattern of an acute myocardial infarction. Liver function was normal.

The electrocardiogram showed ST elevation in leads II, III, aVF, and V5–V6 with T wave inversion and Q wave formation in those leads consistent with inferior infarction (Fig. 2a). His condition stabilised, and cardiac catheterisation performed one week later showed normal coronary arteries and left ventricular function. Radionuclide left ventricular ejection fraction was 64%. An echocardiogram showed no pericardial effusion. An autologous indium^{111} leucocyte scan showed myocardial uptake. A 24 hour electrocardiographic recording showed episodes of sinus tachycardia, multiple unifocal ventricular extrasystoles, and short runs of ventricular bigeminy.

Right ventricular endomyocardial biopsy showed focal lymphocytic infiltrates and associated myofibre necrosis compatible with active myocarditis (Fig. 2b). After an uneventful clinical course, he was discharged in good condition.

Myocardial biopsy was repeated three months later to confirm the resolution of myocarditis before the patient was allowed to resume his usual school and sporting activities. Irregular myocyte hypertrophy, focal myofibril loss, and increased interstitial fibrosis were present. No inflammatory infiltrates were detected. The histological changes were considered to represent healed myocarditis. A follow up electrocardiogram showed persistent T wave inversion in the inferolateral leads. To date the patient is in good health and performs his work without limitations.

Discussion

These two patients had clinical and electrocardiographic evidence of myocardial infarction in the clinical setting of acute myocarditis. Non-invasive imaging with indium^{111} labelled leucocytes and gallium^{67}[9] suggested the presence of myocardial inflammation, which was confirmed by endomyocardial biopsy. The diagnosis of myocarditis was based on the presence of 5 lymphocytes per high power field and associated myocardial necrosis. The foci of active myocarditis identifying unsuspected myocarditis in association from the infarcted area, as defined by the electrocardiogram, emphasising the efficacy of this technique in identifying unsuspected myocarditis in association with unexplained myocardial necrosis. No histological changes suggesting ischaemic heart disease were found. Lymphocytic infiltration and myofibre necrosis were detected in the first patient four months after the acute myocardial infarction, and it is therefore highly unlikely that they represent the histological manifestations of myocardial infarction by themselves. In the first patient, viral infection was the most likely cause of the febrile illness. The chronic corticosteroid treatment for his rheumatoid arthritis may possibly account for the unusually severe myocardial involvement. Myocardial infarction due to rheumatoid coronary vasculitis, in the presence of extensive extra-articular disease and cutaneous vasculitis, has been reported.[10] Our patient, in contrast, had no evidence of extra-articular disease, and the absence of bound immunoglobulin or immune complex deposition in myocardial tissue argues against rheumatoid arthritis as the cause of myocarditis and infarction. This patient had no symptoms suggesting coronary artery spasm. Although this possibility cannot be eliminated, this entity is an unlikely cause of his myocardial infarction. The second patient had a viral syndrome with sore throat, low grade fever, and myalgias. He presented with non-pleuritic chest pain and electrocardiographic and enzymatic evolution typical of an acute myocardial infarction. He did not have a pericardial friction rub or echocardiographic evidence of a pericardial effusion. These abnormalities could not therefore be ascribed to pericarditis or coronary artery disease. The biopsy confirmed active myocarditis as the likely cause of the myocardial necrosis.

The two patients underwent coronary angiography within two weeks of acute myocardial infarction. The possibility of an intracoronary thrombus resulting in acute myocardial infarction and resolving without residual coronary obstruction cannot be excluded. Neither patient, however, had a history of chest trauma, heavy exertion, or excessive smoking, and thus in situ coronary thrombus formation is an unlikely cause of their myocardial infarction.

Careful clinicopathological correlations at necropsy have shown that viral myocarditis has a wide spectrum of clinical presentations. Subsequent to the systemic manifestations of a viral syndrome (fever, upper respiratory infection, myalgias, arthralgias, gastrointestinal complaints) patients with myocarditis may be asymptomatic or develop pericarditis, arrhythmias, progressive circulatory failure or precordial pain, and electrocardiographic changes.[1 2 11] Symptoms and signs, including exertional non-pleuritic chest pain, increased enzyme activity, and the appearance of ST elevation, T wave inversion, and abnormal Q waves in the electrocardiogram indistinguishable from myocardial infarction have also been observed.[12] Nevertheless, histological documentation during life has not previously been reported.

Serological evidence of Coxsackie B virus infection in man has been identified in 10–18% of patients with documented myocardial infarction. These data are not consistent and vary with the patient population, assay method, and sampling times.[13 14] The confusion surrounding the association of myocardial infarction with myocarditis is perpetuated by the lack of unequivocal documentation of the latter process after acute myocardial infarction occurring in the setting of acute viral infection.

In the experimental model, a necrotising transmural myocarditis has been produced in mice infected with Coxsackie virus B1 or B4. Several weeks after infection, 10% of the animals had aneurysmal dilatation of the left ventricle. Myocardial thinning, necrosis, and normal coronary vessels were found in the affected areas.[5] These findings strongly suggest that some ventricular aneurysms may represent complications of a preceding unrecognised necrotising myocarditis and may parallel similar findings in man.

Based on our findings, selected patients with clinical, electrocardiographic, and laboratory evidence of myocardial infarction but normal coronary arteries, in whom coronary artery spasm or a resolved intracoronary thrombus are unlikely, may be considered for inflammation-avid isotopic imaging and endomyocardial biopsy to identify myocarditis associated with myocardial necrosis. After resolution of the acute event, if inflammation and cardiac dysfunction persist, treatment designed to suppress inflammatory response may be appropriate.[15]

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Is there an indication for coronary angiography in patients under 60 years of age with no or minimal angina pectoris after a first myocardial infarction?

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SUMMARY Coronary angiography and exercise stress tests were performed in 91 consecutive patients under 60 years of age having either no or only mild angina pectoris with or without medication after a first myocardial infarction. Nine (10%) patients had angiographic high risk coronary artery disease defined as three vessel disease, left main stenosis, or proximal stenosis of the left anterior descending artery. Eighteen patients had a positive electrocardiographic exercise stress test, including eight of the nine patients with angiographic high risk coronary artery disease.

It may be concluded therefore that coronary angiography to detect high risk coronary artery disease in this group can be restricted to patients with a positive exercise stress test. This policy would obviate the need for about 80% of coronary angiograms performed in this age group.

The indication for coronary angiography in patients after a first myocardial infarction, with no or only mild angina pectoris, remains controversial.[1–6] In patients with severe angina, there is a clear indication for coronary angiography to determine their suitability for surgery. Although patients with no or only mild angina pectoris are not candidates for coronary artery bypass surgery on the basis of symptoms, severe coronary artery disease may be present despite their apparently minor symptoms.[6–8] In some cardiac centres all patients under a certain age with evidence of coronary artery disease in the absence of specific contraindications are examined by coronary angiography in order to detect high risk disease.

High risk coronary artery disease is defined as: three vessel disease, proximal stenosis of the left anterior descending artery, or stenosis in the left main coronary artery (see methods). In these patients surgery has been shown to prolong life expectancy.[9–16] Our study was performed in order to determine the incidence of high risk coronary artery disease in patients under 60 years of age without or with only mild angina pectoris after a first myocardial infarction and whether or not the existence of high risk coronary artery disease could be predicted from the results of electrocardiographic exercise stress testing.

Patients and methods

PATIENT SELECTION

Only patients, under 60 years of age, who sustained a first transmural myocardial infarction in the period January 1982 to October 1983, with no or with only mild angina pectoris (New York Heart Association functional class I or II for angina pectoris) irrespective of treatment were considered eligible. Patients with valvar heart disease, congestive heart failure, left bundle branch block, or associated severe non-cardiac disease such as malignancy, insulin dependent diabetes, or severe hypertension were excluded from the study. Cardiac catheterisation and coronary angiography were performed about two months after acute myocardial infarction. Ninety one patients entered the study. Before cardiac catheterisation and coronary angiography all patients underwent electrocardiographic exercise testing. If patients were receiving medication this was not withdrawn.

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EXERCISE TESTING

All patients underwent a symptom limited exercise stress test to detect a possible discrepancy between subjective and objective signs of coronary insufficiency. The stress test was performed using either a treadmill (with the graded multistage exercise protocol of Bruce) or a graded bicycle ergometric exercise test (10 W/min). Every three minutes a complete 12 lead electrocardiogram was recorded and blood pressure measured.

In the absence of electrocardiographic signs of coronary insufficiency, irrespective of whether or not patients reached 85% of the predicted maximal heart rate, the stress test was considered to be negative. The test was considered to be inconclusive if the electrocardiogram showed ST segment elevation in leads over the infarcted area accompanied by reciprocal ST segment depression. Several authors have attributed these ST segment elevations to abnormal left ventricular wall motion.[17-19]

Electrocardiographic signs of coronary insufficiency were defined as: *(a)* J point depression of $\geq 0 \cdot 1$ mV relative to the end of the PQ segment, with horizontal or downward sloping ST segment,[20 21] or *(b)* U wave inversion,[22] or *(c)* a slow upsloping ST segment depression $\geq 0 \cdot 2$ mV for at least 0·08 s beyond the J point,[23 24] or *(d)* an increase of $\geq 0 \cdot 2$ mV for at least 0·08 s after the J point in cases of preexisting ST segment depression.

LEFT VENTRICULOGRAPHY AND CORONARY ANGIOGRAPHY

The left ventricle was visualised in the frontal and lateral projections. The segmental contractililty was classified as normal, hypokinetic, akinetic, or dyskinetic. Coronary angiography was performed by either the Sones' or Judkins' technique. In addition to the standard posterior-anterior and oblique projections, angulated views were also used.

In patients with normal coronary arteries an ergonovine provocation test was performed 48 hours after stopping all medication. Increasing doses of 0·05, 0·1, and 0·2 mg ergonovine maleate were injected intravenously under electrocardiographic control and recording of symptoms.

Coronary stenoses resulting in more than a 70% reduction of luminal diameter in any projection were considered to be haemodynamically important.[25 26] Only the most severe narrowing in each coronary artery was counted. Left main stenosis was counted as two vessel disease and was considered to be present when the luminal diameter was reduced by more than 50%, as commonly accepted. Stenoses of angiographically large diagonal or marginal branches were considered as lesions of the left anterior descending and circumflex coronary arteries respectively. Patients were classified as having one vessel, two vessel, or three vessel disease.

High risk coronary artery disease was defined as: *(a)* three vessel disease—all vessels having a narrowing >70%, *(b)* left main stenosis >50%, *(c)* proximal stenosis of the left anterior descending artery with a 70–99% narrowing before take off of the first large septal perforator without prior anterior wall infarction, and *(d)* any combinations of the above.

STATISTICAL METHODS

The results were analysed by the χ^2 test. A p value $<0 \cdot 05$ was considered to be significant.

Results

CLINICAL CHARACTERISTICS

The mean age of the 91 patients (88 men, three women) was 48 (range 34–59) years. Of these, 51 sustained an inferior wall infarction and 40 an anterior wall infarction. Seventy patients were in NYHA functional class I and 21 in functional class II for angina pectoris (Table 1).

FINDINGS AT CORONARY ANGIOGRAPHY

Table 2 summarises the findings.

All patients—Four patients had completely normal vessels, including one with an aberrant origin of the right circumflex artery. Another patient had <70% stenoses. All these patients underwent an ergonovine provocation test, which appeared to be negative in all cases. High risk coronary artery disease was present in nine patients; four had left anterior descending artery stenosis and five three vessel disease, including two patients with associated left main stenosis.

Functional class—High risk coronary artery disease was present in five out of 70 asymptomatic patients (class I) and in four out of 21 with mild angina pectoris (class II). This difference is not significant. Two patients with left main artery stenosis were asymptomatic.

Site of infarction—Seven out of nine patients with high risk coronary artery disease had sustained an inferior wall infarction: four patients had proximal stenosis of the left anterior descending artery and three had three vessel disease, including the two patients with left main stenosis. None of the patients

Table 1 *NYHA functional class of symptoms related to the site of the infarction*

Site	*No of patients*	*Class I*	*Class II*
Inferior	51	39	12
Anterior	40	31	9
Total	91	70	21

Table 2 *Angiographic findings*

No of diseased vessels	*No of patients*	*Including stenosis of:*	
		Left anterior descending artery	*Left main artery*
		All patients (n=91)	
0	5	—	—
1	63	—	—
2	18	4*	—
3	5*	—	2*
		Patients in class I (n=70)	
0	5	—	—
1	49	—	—
2	14	3*	—
3	2*	—	2*
		Patients in class II (n=21)	
0	0	—	—
1	14	—	—
2	4	1*	—
3	3*	—	—
		Patients with inferior infarction (n=51)	
0	1	—	—
1	36	—	—
2	11	4*	—
3	3*	—	2*
		Patients with anterior infarction (n=40)	
0	4	—	—
1	27	—	—
2	7	—	—
3	2*	—	—

*High risk coronary artery disease.

with previous anterior wall infarction had left main disease or proximal stenosis of the left anterior descending artery in the sense of high risk disease. If the left anterior descending artery was occluded or supplied the infarcted area this was not considered to be in the high risk category. The difference in the incidence of high risk disease between patients with previous inferior or anterior wall infarction was not significant.

EARLY COMPLICATIONS OF CARDIAC CATHETERISATION

Three patients developed early complications after catheterisation: one required surgical correction of a pseudoaneurysm of the femoral artery, and two had reversible glottic oedema and shock attributable to an allergic reaction to the contrast material.

FINDINGS AT EXERCISE STRESS TESTING

Nine of the 70 patients who were in functional class I had a positive stress test as did nine of the 21 patients in class II (Table 3). This difference is significant ($p<0{\cdot}01$). All patients showed a normal blood pressure response during exercise. No attempt was made to record the differences between maximal heart rate and duration of exercise in relation to the method of stress testing used.

Only six patients with one vessel disease had a positive stress test, whereas all the patients with three vessel disease, including two with left main stenosis, had a positive exercise response. Three of the four patients with proximal stenosis of the left anterior descending artery had a positive stress test. None of the patients with an inconclusive test had high risk disease.

In 18 patients the exercise test was positive, including eight of the nine patients with high risk disease. Only one patient with high risk disease had a negative stress test. The difference in incidence of high risk disease in patients with a positive exercise test compared with those with a negative test is significant ($p<0{\cdot}001$).

Thirteen of 15 patients with an inconclusive test had previously sustained an anterior wall infarction and two an inferior wall infarction. After previous anterior wall infarction 10 patients had one vessel disease and three two vessel disease. Of the remaining two patients after inferior wall infarction, one had one vessel disease and the other two vessel disease. At left ventriculography dyskinesia of the infarcted area was found in 12 patients and akinesia in three.

Discussion

This study was performed to document angiographically the incidence of high risk coronary artery disease in patients under 60 years of age having no or only mild angina pectoris after first transmural myocardial infarction and to relate this to the results of exercise stress testing.

Table 3 *Results of exercise stress test in relation to functional class and number of diseased vessels*

Variable	*No of patients*	*Test result:*		
		Positive	*Negative*	*Inconclusive*
Functional class:				
I	70	9	49	12
II	21	9	9	3
Total	91	18	58	15
No of diseased vessels:				
0	5	0	5	0
1	63	6	46	11
2	18	7*	7†	4
3	5	5	0	0

*Including three patients with stenosis of the left anterior descending artery.
†Including one patient with stenosis of the left anterior descending artery.

Previous studies—the European coronary surgery study group,[12] the Veterans Administration study,[10] the Seattle Heart Watch,[11] and Sheldon *et al*[16]—suggest that life expectancy might be prolonged by operation in patients with stable angina pectoris and associated left main stenosis, three vessel disease, or proximal left anterior descending stenosis. On the other hand the latest Coronary Artery Surgery Study fails to show an improved five year survival after coronary artery bypass surgery in patients with no or mild angina pectoris with either three vessel disease or proximal left anterior descending artery stenosis.[27] Nevertheless, as only 37% of the patients who were eligible were actually studied, the question of whether these results are valid remains.

Comparison of our results with other reported studies is hampered by differences of definition as to what constitutes a haemodynamically important stenosis (Table 4). Mautner and Phillips considered a >70% cross sectional narrowing haemodynamically important, corresponding to a 50% narrowing in luminal diameter.[28] Vanhaecke *et al* considered a >50% diameter narrowing as haemodynamically important.[29] For the purposes of this study we chose a >70% reduction in luminal diameter as being haemodynamically important. These differences probably explain the lower incidence of three vessel disease in our study, which is similar to that reported by Roubin *et al*[30] (Table 4). The higher incidence of one vessel disease in our series might possibly be due to our criteria for patient selection. Firstly, all patients were under 60 years of age (mean 48 years). Chaitman *et al* reported a higher incidence of multivessel disease in patients over 55 years.[31] In David's series, 18% of patients under 40 years of age had normal coronary angiograms.[32] Secondly, all patients had recently sustained a first infarction. Roubin *et al* found a higher incidence of three vessel disease after second infarction.[30] Thirdly, our patients had only mild or no angina, whereas Vanhaecke *et al* and Chaitman *et al* found a higher incidence of three vessel disease in patients with more severe symptoms.[29 31]

In the present study five of 70 patients without angina pectoris had high risk disease compared with four out of 21 with mild angina. This difference is not significant.

Several reports suggest a higher incidence of multivessel disease in patients after inferior wall infarction.[31 33] In our study 14 out of 51 patients who sustained inferior wall infarction had multivessel disease, including three with three vessel disease. Although nine of 40 patients after anterior wall infarction had multivessel disease, including two with three vessel disease these differences are not significant, as confirmed by Roubin *et al*, who also found no difference in the incidence of multivessel disease in patients with inferior wall infarction compared with patients with anterior wall infarction.[30]

Although the risk of morbidity related to cardiac catheterisation is low 2–3%,[34 35] the mortality, nevertheless, amounts to 0·2%.[34 35] Bourassa and Noble found that mortality was closely related to the presence of left main coronary artery stenosis.[35] In our study no patient died, and the complication rate was 3%.

All patients with three vessel disease, including the two with left main stenosis, had a positive exercise stress test, even when taking medication. This agrees with the results of Weiner *et al*, who, using only a horizontal ST segment depression of >0·1 mV, found that 97% of the patients with left main stenosis and 96% of the patients with three vessel disease had a positive result.[36] Similarly three of the four patients with a proximal left anterior descending artery stenosis had a positive stress test, which is in accordance with the results of Chaitman *et al*, who found a positive test in 86% of the patients with proximal left anterior descending artery stenosis.[31]

It would, therefore, appear that the existence of left

Table 4 *Review of published studies*

Author	*No of patients*	*Definition of significant stenosis*	*Patient characteristics*	*% Of patients with*:*			
				Normal vessels	*One vessel disease*	*Two vessel disease*	*Three vessel disease*
Roubin *et al*[30]	202	>70% diameter narrowing	No, mild, or severe angina, <60 years	7	62	24	7
Mautner and Phillips[28]	31	>70% cross sectional narrowing	No or only mild angina, <65 years	7	32	32	29
Vanhaecke *et al*[29]	59	>50% diameter narrowing	No angina, <45 years	51		49	
Present study	91	>70% diameter narrowing	No or only mild angina, <60 years	5½	69	20	5½

*Although the use of percentages calculated from populations of <100 is often misleading, vessel involvement is given as a percentage for comparison.

main stenosis, three vessel disease, and in most cases also proximal left anterior descending artery stenosis can be predicted on the basis of a positive exercise test.

CONCLUSION

The indication for coronary angiography in patients under 60 years who have sustained a first myocardial infarction and who subsequently are either asymptomatic or have only mild angina pectoris is still controversial. Our study suggests that high risk coronary artery disease is seldom encountered in such patients. The presence of high risk disease is almost always associated with a positive exercise stress test. Although no mortality was associated with angiography in this study group, a 3% early complication rate cannot be overlooked. Thus, bearing in mind both patient safety and cost containment, we conclude that in this patient population coronary angiography to detect high risk disease should be limited to patients with a positive exercise test. This policy could be expected to save approximately 80% of angiograms in this patient population.

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Comparative recognition of left ventricular thrombi by echocardiography and cineangiography

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SUMMARY Studies performed in 47 patients, 11 of whom underwent surgery for aneurysmectomy and 36 of whom underwent cardiac transplantation, were reviewed to assess the diagnostic accuracies of cross sectional echocardiography and cineangiography in detecting left ventricular mural thrombi and the effect of anticoagulation treatment on the incidence of such thrombi. Cross sectional echocardiography in 37 patients and cineangiography in 26 (16 patients were examined by both methods) were analysed independently by sets of two observers experienced in the respective methods. All four observers were blinded to the pathological or surgical findings regarding mural thrombus. Mural thrombus was confirmed by pathological investigation in 14 of 47 (30%) cases; 11 of these 14 patients had intra-aneurysmal thrombi. The negative predictive value was quite good for both methods, but cross sectional echocardiography had a superior positive predictive value. This was due both to detailed soft tissue resolution by cross sectional echocardiography and to overdetection of mural thrombi by cineangiography in cases of aneurysms without mural thrombi. Mural thrombi were present in three of 20 patients with preceding anticoagulation and in 10 of 19 patients without anticoagulation. The results emphasise that cross sectional echocardiography is more reliable than cineangiography in recognising thrombi.

Recognition of left ventricular mural thrombi may be important before cardiac surgery or when anticoagulation treatment is considered. Recent experience has shown that cross sectional echocardiography is useful in detecting left ventricular thrombi.[1–6] Left ventricular cineangiography has also been used to diagnose this problem.[7 8] There have, however, been few systematic studies to examine the diagnostic accuracy of either cross sectional echocardiography or cineangiography in the detection of mural thrombi.[9–13] In addition, controversy continues regarding the relative superiorities of echocardiography and angiography in the diagnosis of mural thrombi. This study is a retrospective analysis of the diagnostic accuracy of the two methods.

Patients and methods

Between January 1980 and March 1983, 107 patients underwent open heart surgery for aneurysmectomy or heart transplantation at Stanford University Medical Center. Fifty six of these patients underwent either cross sectional echocardiography or angiography or both at Stanford before surgery and were our initial study population. In this group five patients who had technically limited echocardiograms or angiograms were excluded, and another four were finally excluded because definite pathological confirmation regarding mural thrombi was not available. Finally, 47 patients (11 undergoing aneurysmectomy and 36 heart transplantation) were available for our study. They comprised six women and 41 men with a mean (SD) age of 41 (15) years.

CROSS SECTIONAL ECHOCARDIOGRAPHY

Cross sectional echocardiography was performed in 37 patients within five (1·8 (1·7)) months before surgery with a Hewlett Packard model 77020A, Toshiba

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SSH-10A, or Irex System III ultrasound imaging system, using a 2·5 MHz or 3·5 MHz medium or short focused transducer. Echocardiograms were interpreted independently by two experienced observers who were blinded to the radiological, pathological, or surgical findings regarding thrombus. The cross sectional echocardiographic criteria for mural thrombi were: *(a)* one or more masses of echoes adjacent to the left ventricular wall but distinct from the endocardial echo; *(b)* different visual texture of echoes from the adjacent myocardium; *(c)* asynergic motion of the adjacent ventricular myocardium; *(d)* occasional mobile projections from the mass into the ventricle; and *(e)* location of the abnormal echoes, usually at the apex. After the initial blind reading had been done by each observer the final decision on the presence or absence of mural thrombi was made by consensus.

LEFT VENTRICULAR CINEANGIOGRAPHY

Left ventriculography was performed in the 30° right anterior oblique projection at 60 frames/s with high resolution caesium iodide intensifiers (Siemens or General Electric). Cine recording of radio-opaque grids at the end of every case verified a minimum of two line pairs/mm resolution. Cineangiography was performed in 26 patients within five (1·6 (1·5)) months before the operation and was analysed independently by two experienced radiologists who also were blinded to the echocardiographic, pathological, or surgical information. A final decision was made by consensus. The diagnosis of mural thrombi by contrast ventriculography was based on *(a)* a filling defect persisting throughout the cardiac cycle and *(b)* a smooth ventricular outline with apparent truncation or loss of normal left ventricular shape.

PATHOLOGICAL AND SURGICAL CONFIRMATION

The pathology reports reviewed for this project included the presence, absence, size, location, and general histological findings of the mural thrombi as well as reports of any associated ventricular aneurysm. In the event that necessary information was missing from a patient's initial pathological report on file, hearts from the transplant recipients were re-examined by the pathologist for the purpose of this study. Surgical findings of mural thrombi during aneurysmectomy were available in the patient's medical records in the operative reports.

STATISTICAL ANALYSIS

Sensitivity was calculated as true positive/(true positive + false negative) × 100(%); specificity as true negative/(true negative + false positive) × 100(%); positive predictive value as true positive/(true positive + false positive) × 100(%); and negative predictive value as true negative/(true negative + false negative) × 100(%). Fisher's exact probability test was used to compare the interobserver differences in the analysis of the presence or absence of mural thrombi by echocardiography and cineangiography. The incidence of mural thrombi in the group treated with anticoagulant agents and the untreated group was compared using χ^2 analysis with Yates's correction.[14] Significance was defined as a p value $<0·05$.

Results

Of the 47 patients studied, 24 had coronary artery disease, 19 primary idiopathic cardiomyopathy, two valvar heart disease, and two congenital heart disease. A left ventricular thrombus was confirmed in 14 of the 47 (30%). The incidence of mural thrombi in coronary artery disease and in cardiomyopathy was 50% (12 out of 24) and 11% (two out of 19) respectively. Eleven of the 12 thrombi in the patients with coronary artery disease were within aneurysms. The sizes of the thrombi varied from 1·5 cm^3 (2·0×1·5×0·5 cm) to 65 cm^3 (radius 2·5 cm, sphere). The thrombi noted in the two patients with cardiomyopathy were both remarkably large with partial adhesion to the left ventricular wall and extension well into the ventricle. Thirteen thrombi were located in the apex and one at the posterior wall; 11 (79%) of the 14 thrombi were intra-aneurysmal. All the thrombi seen in the aneurysms were overlying the aneurysm bed and were firmly attached to the scarred myocardium or were identified under an endothelialised surface of the organised thrombus. The thrombi associated with myocardial aneurysms were all laminated and did not protrude into the ventricle.

There was observer disagreement regarding the interpretation of mural thrombi on echocardiograms in five cases (the consensus reached was two positive and three negative) and on cineangiograms in four cases (consensus reached was all four negative). The interobserver differences were not significant.

CROSS SECTIONAL ECHOCARDIOGRAPHY

Of the 37 patients evaluated by cross sectional echocardiography, 10 had true positive cases of mural thrombi, three false positive, 22 true negative, and two false negative. Thus sensitivity was 83%, specificity 88%, positive predictive value 77%, and negative predictive value 92%. In the true positive cases the actual sizes of mural thrombi, as determined by pathological investigation, were closely estimated by the measurements made with cross sectional echocardiography (Fig. 1). A large mural thrombus was, however, appreciably underestimated in size in one instance (Fig. 2). The smallest mural thrombus detected by cross sectional echocardiography was 2×2×1·5 cm. Mural thrombi were clearly differenti-

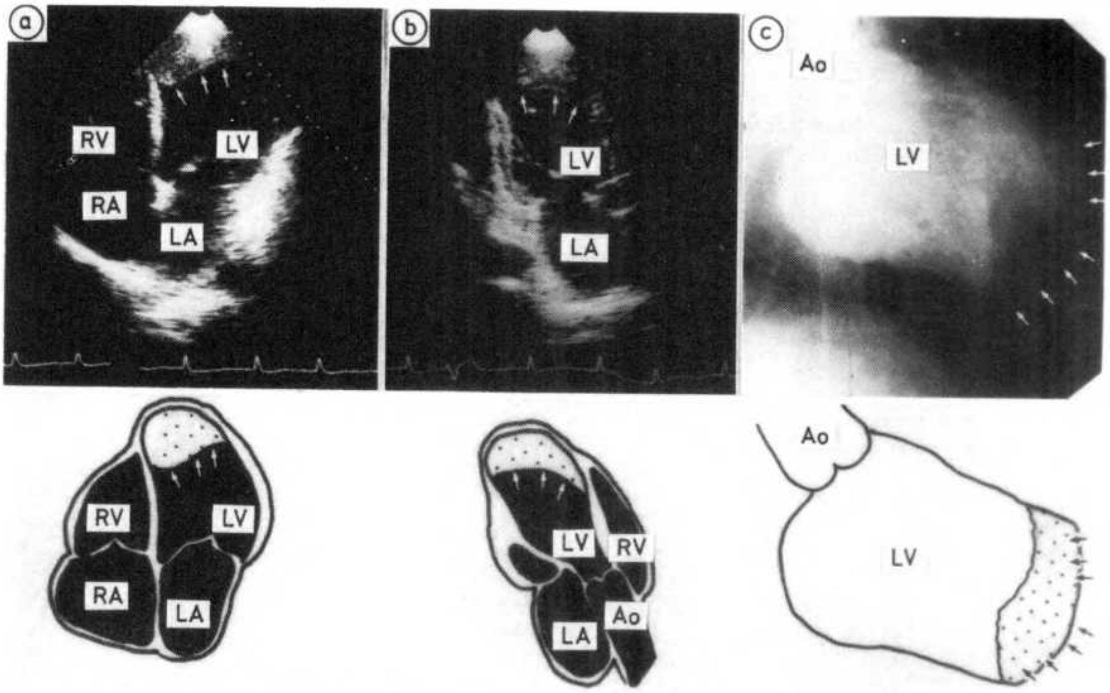

Fig. 1 *Echocardiograms in the (a) apical four chamber view and (b) apical long axis view and (c) a right anterior oblique angiogram in a 65 year old man with extensive anterior myocardial infarction. Both cross sectional echocardiography and cineangiography were performed within a week before surgery. A mural thrombus at the apex is seen (arrows) in (a) and a sharp cut off of contrast distant from the apex (arrows) in (c). Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Schematic drawings are provided for illustration (lower panels).*

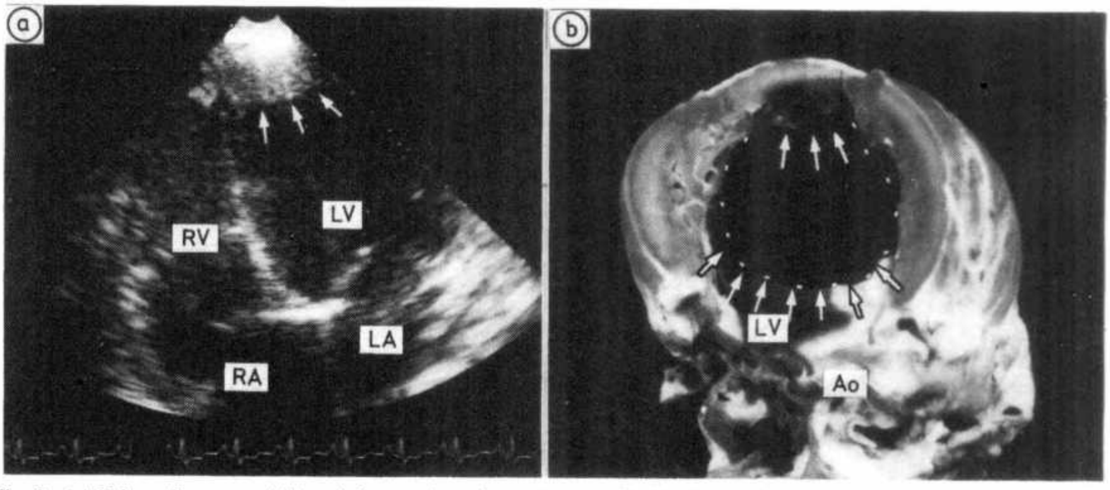

Fig. 2 *(a) Echocardiogram and (b) pathology specimen from a 14 year old girl with cardiomyopathy. (a) The echo was read as positive in the apical four chamber view but the thrombus was appreciably underestimated in size (arrows). (b) A large spherical thrombus (dots and arrows), virtually filling the ventricle, was found at surgery for heart transplant performed three days after the echocardiographic study. The pathology specimen has been oriented to place the apex as in the echocardiogram. The planes of section are different, but the huge thrombus is spherical so this could not account for the disparity in size. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; Ao, aorta.*

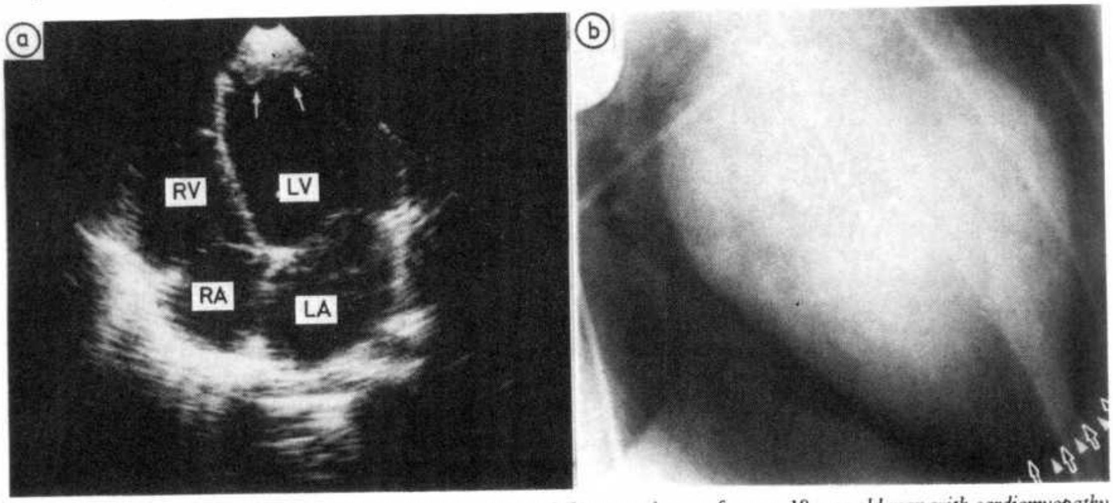

Fig. 3 *(a) Echocardiogram in the apical four chamber view and (b) an angiogram from an 18 year old man with cardiomyopathy. (a) A mass of echoes at the apex was noted (arrows), but this corresponded to localised thick scar tissue without thrombus by pathology (false positive study by echocardiography). (b) No irregularity of the apex (arrows) was noted (true negative case). RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle.*

ated from papillary muscles and muscle bands by their size, shape, and location. The pathological findings in the two patients with false negative thrombi both showed small thin thrombi attached to the apical endocardium, which were not visible on our echo studies. Endocardial fibrosis and localised thickened scar tissue without thrombi were found to be the basis of the false positive diagnoses (Fig. 3). Localised calcium in a mass of echoes at the ventricular apex was noted in one false positive case, in which the calcium was in pure scar tissue without associated thrombus.

CINEANGIOGRAPHY

Of the 26 patients who underwent cineangiography, five had true positive, six false positive, 12 true negative, and three false negative cases of mural thrombus. Thus sensitivity of the technique was 63%, specificity 67%, positive predictive value 45%, and negative pre-

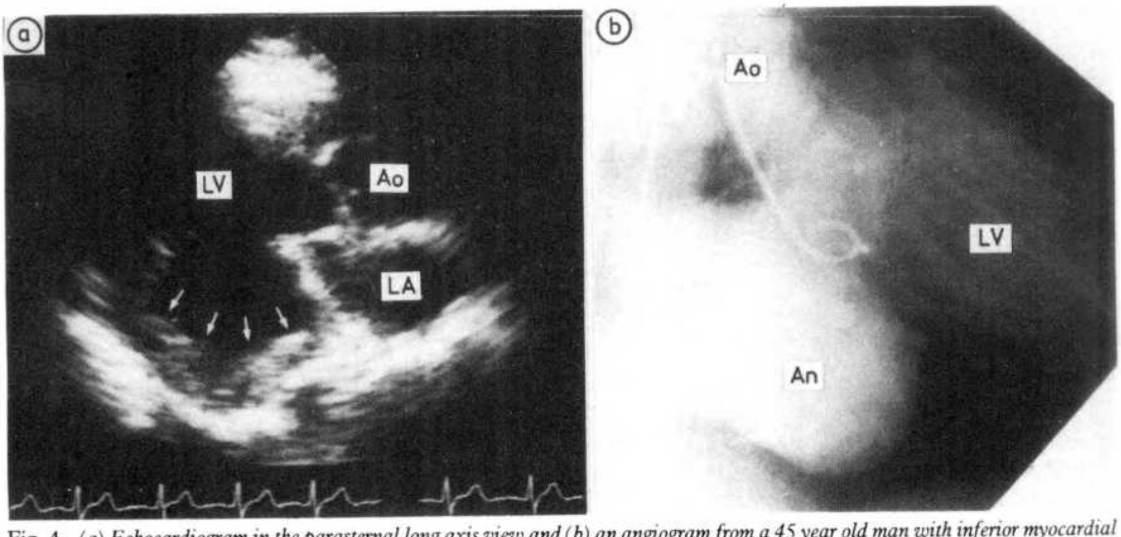

Fig. 4 *(a) Echocardiogram in the parasternal long axis view and (b) an angiogram from a 45 year old man with inferior myocardial infarction. (a) A thick layered thombus (arrows) is shown in a posterior wall aneurysm. (b) The contour of the aneurysmal (An) sac is smooth and no filling defect is apparent. This was a false negative study by angiography. LV, left ventricle; LA, left atrium; Ao, aorta.*

dictive value 80%. In all three false negative and four of six false positive cases there were associated left ventricular aneurysms. Thus most cases of misdiagnosis of mural thrombi by cineangiography were related to the presence of ventricular aneurysms (Fig. 4). The relatively high number of false positive cases resulted from the misinterpretation of contrast filling defects caused by aneurysms with rough surfaces and abnormalities of segmental wall motion. The factors related to the relatively low sensitivity of angiography compared with cross sectional echocardiography were obscuration of small mural thrombi or incomplete mixing of contrast medium within the apex. The factors related to the low positive predictive value were difficulties in distinguishing trabeculation from mural thrombi (one case), irregular ventricular contour due to prior aneurysmectomy (one case), and aneurysms with irregular walls (four cases).

ANTICOAGULATION TREATMENT AND MURAL THROMBI

Information regarding the presence or absence of anticoagulation treatment was available in 39 patients. Sodium warfarin, heparin, sulphinpyrazone, or dipyridamole were considered to be anticoagulants. Mural thrombi were present in three of 20 patients who had received at least four weeks' treatment with anticoagulants before heart surgery and in 10 of 19 patients who had not received anticoagulants ($p<0·05$). Treatment with anticoagulants was begun after primary embolic events in four patients. None of these patients had subsequent emboli. Ventricular thrombus was sought and found by echocardiography in only one patient at the time of primary embolism.

Discussion

The presence of left ventricular mural thrombi may be assessed by several diagnostic methods including angiography, M mode and cross sectional echocardiography, radionuclide scintigraphy, and computed tomography. The first angiographic observation of mural thrombi in coronary artery disease is attributed to Hamby *et al* in 1974.[7] They showed the angiographic features of mural thrombi: "the apex appeared sharply cut off during both diastole and systole," and "the apex appeared completely obliterated by an irregular, non-uniform density." The early experience with M mode echocardiography showed a limited ability of this method to detect apical mural thrombi except when thrombi protruded into the left ventricle.[15–17] Cross sectional echocardiography has proved to have an advantage in recognising mural thrombi that are predominantly at the ventricular apex. Previous studies, however, were done with early equipment, and uniform criteria for mural thrombi by either echocardiography or cineangiography were not established previously.[1–3 18 19] Our study was performed with generally accepted criteria on images of high quality from modern angiographic and echocardiographic instruments. Ezekowitz *et al*[20] and Stratton *et al*[21] reported their experience with radionuclide scintigraphy (platelets labelled with indium-111) for detecting left ventricular thrombi as highly specific (specificity 88–99%) but with relatively low sensitivity (60–77%). Computed tomography, as reported by Godwin *et al*[22] and Tomoda *et al*,[23] had soft tissue resolution that allowed them to distinguish thrombi from the ventricular wall. Tomoda *et al* reported computed tomography with a sensitivity of 100% and a specificity of 91% for detecting left atrial thrombi but did not refer to left ventricular thrombi.[23] Both this type of radionuclide scintigraphy and computed tomography are, however, expensive, and facilities for performing them are not generally available.

LIMITATIONS OF CROSS SECTIONAL ECHOCARDIOGRAPHIC DIAGNOSIS

The diagnostic accuracy of cross sectional echocardiography for mural thrombi in our series (sensitivity 83%, specificity 88%) was in the range previously reported (sensitivity 72–95%, specificity 86–90%) by others.[9–11] The size and location of mural thrombi were well estimated by cross sectional echocardiography, except in one case of a large fresh homogeneous thrombus (Fig. 2). The discrepancy in this case between the echocardiographic and pathological findings was probably because of the low and uniform echogenicity of the fresh thrombus.[24 25] The reasons for the misinterpretations of thrombi by echocardiography, compared with pathological findings, have been discussed in the results section and may be limitations that can be addressed by further improvements in diagnostic echocardiography. We found that the medium range focused transducers occasionally masked the near field with extraneous echoes at standard gain settings. We have recently used both medium (6–8 cm) and short (2–5 cm) focused transducers routinely when abnormal echoes have been suspected in the ventricular apex. A short focused transducer may help in difficult or equivocal cases by improving the image in the area near the transducer.

LIMITATIONS OF ANGIOGRAPHIC DIAGNOSIS

The diagnostic accuracy of angiography for mural thrombi in our series (sensitivity 63%, specificity 67%) was in the range of previous reports (sensitivity 31–73%, specificity 75–92%).[12 13] The relatively lower diagnostic accuracies of angiography compared with echocardiography may have been due to lower resolution, even with state of the art angiographic equipment, or inadequate criteria for distinguishing mural thrombi from the left ventricular wall. False negative studies may be explained by the absence of a filling defect in a laminated type of mural thrombus or contrast surrounding a small thrombus. Over detection of mural thrombi (false positive studies) may have occurred owing to an irregular contour of the left ventricular wall caused by trabeculae, muscle bands, or associated aneurysms without thrombi.[26] Our study showed low positive predictive value (45%) similar to the findings (57%) of Reeder *et al.*[12]

ANTICOAGULATION TREATMENT

Since 1950 there have been arguments concerning the effectiveness of anticoagulation treatment for preventing the formation of mural thrombi and embolic phenomenon in high risk patients with coronary artery disease.[27] We found a significant difference ($p<0{\cdot}05$) in the incidence of thrombi between the patients who had received anticoagulation treatment for at least four weeks and those who had not. These results were similar to Keating *et al*'s data[28] but differed from those of Simpson *et al*[29] and Swan *et al.*[30] None of the five patients who had embolic events in our series had received previous anticoagulation treatment. Information regarding the dose, duration, interruption, or absence of anticoagulation treatment in patients without embolic events was not, however, uniformly obtainable throughout the follow up period, so a statistical comparison could not be made. Kallichurum *et al* reported a prevalence of emboli noted in lung, kidneys, spleen, myocardium, and brain as high as 58% in patients with cardiomyopathy at postmortem studies.[31] Our study included only clinically manifest emboli.

As this study was performed retrospectively, it has some limitations: *(a)* the lack of uniformity of the examination technique in both cross sectional echocardiography and angiography; *(b)* the limited number of patients (16 out of 47) examined by both echocardiography and cineangiography; and *(c)* the time between the examination date and date of operation. Attempts to standardise the examination technique in our laboratory have, however, been emphasised since 1979.[32] Direct comparison of the two methods in the same patients would have been optimal, but the 16 patients examined by both techniques are of special interest in view of the false positive results by angiography: of the four angiographically false positive cases, two were correctly interpreted as negative and two were also falsely positive by echocardiography. Finally, chart and pathological report reviews did not lead us to believe that gross embolism of mural thrombus developed between echocardiographic or angiographic study and examination by pathology or surgery.

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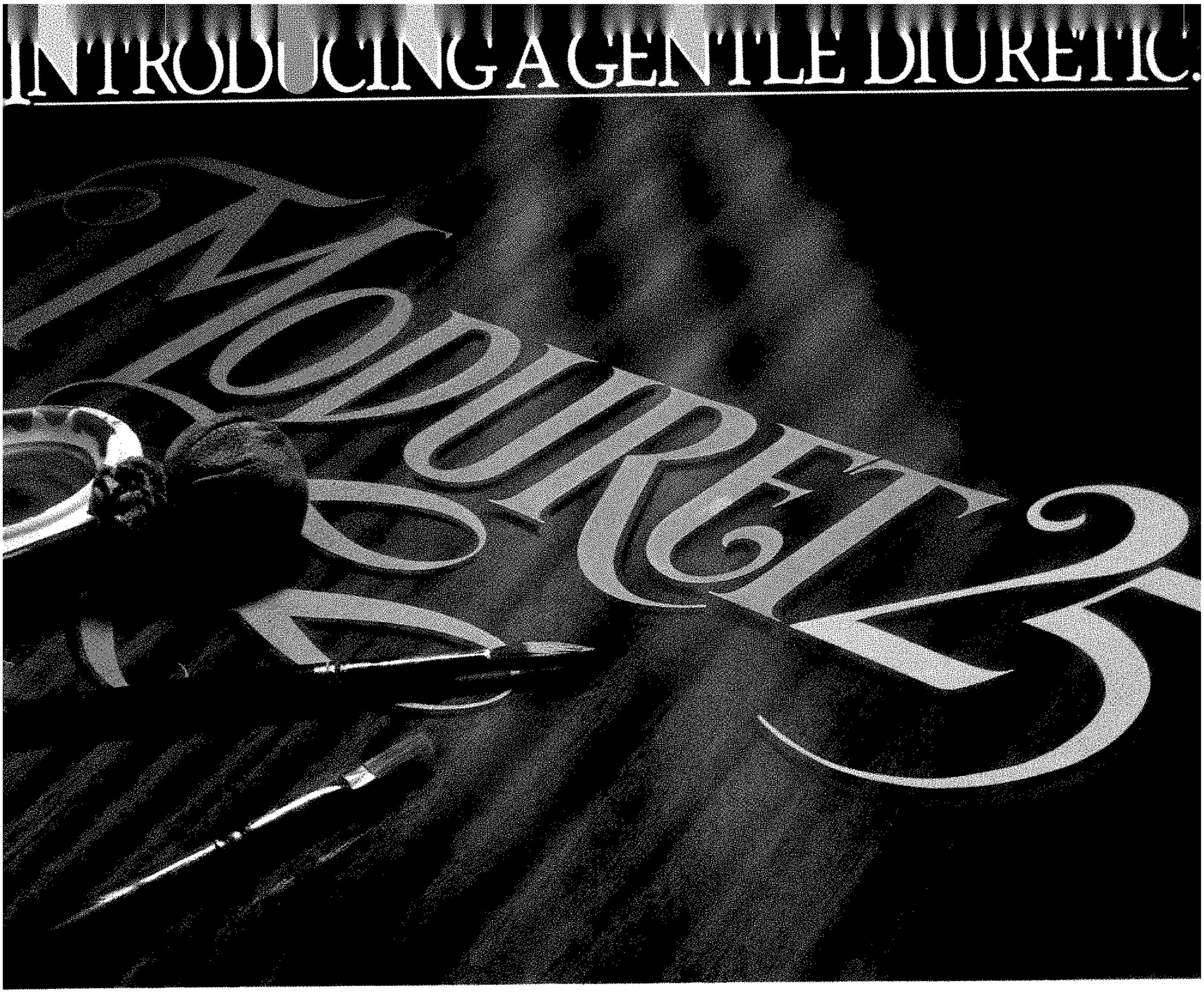

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Br Heart J 1985; **53**: 43–6

Beneficial effects of diltiazem and propranolol, alone and in combination, in patients with stable angina pectoris

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SUMMARY The antianginal effects of diltiazem 180 mg/day and propranolol 240 mg/day, alone and in combination, were investigated in 15 patients with effort related angina in a double blind placebo controlled crossover trial, with each period of treatment lasting four weeks. Patients performed a symptom limited treadmill exercise test at the end of each period of treatment. Mean (SEM) time to onset of angina was increased from 293(32) s when receiving placebo to 347(38) s when receiving diltiazem alone, to 350(30) s when receiving propranolol alone, and further to 421(34) s when receiving diltiazem and propranolol combined. Similar changes occurred in the duration of exercise testing and time to 1 mm ST segment depression. The sum of ST segment depression at peak exercise was reduced by both diltiazem and propranolol alone compared with placebo, and combination treatment produced a further significant improvement. Rate pressure product was significantly reduced at rest and at peak exercise after propranolol alone and combination treatment. The study clearly showed the superior value of diltiazem and propranolol combined in effort related angina when compared with either drug used alone.

Until the advent of calcium channel blocking agents, beta adrenergic blocking agents in combination with nitrates had been the standard medical regimen for stable angina pectoris. Calcium channel blocking agents have proved to be an important advance in the management of ischaemic heart disease. They achieve their effect by interfering with the transmembrane transport of calcium ions in various tissues.[1] Because of their ability to inhibit smooth muscle contraction they are effective in angina due to coronary artery spasm. Used alone they are also effective in chronic effort related angina pectoris and thus provide a useful form of treatment in patients in whom the use of beta adrenergic blockers is contraindicated.[2 3] Several studies have shown, however, that when a calcium channel blocking agent is added to a beta adrenergic blocker in the treatment of stable angina the combination is more effective than when either drug is used alone.[4 5]

Diltiazem is a calcium channel blocking agent that has been shown to improve exercise tolerance in stable angina pectoris.[6 7] Calcium channel blocking agents are, however, a heterogeneous group of drugs differing in both molecular structure and in their pharmacological actions.[8] Diltiazem may have potential advantages over the other presently available calcium channel blocking agents. It can produce vasodilatation without increasing heart rate, has a low incidence of side effects, and can be given both intravenously and by mouth. In addition, studies in dogs have shown that it has a less negatively inotropic effect than verapamil or nifedipine.[9] Thus its effects when combined with beta blockade may differ from those of other available calcium channel blockers. We undertook this study to evaluate the effects of diltiazem when combined with propranolol in chronic exertional angina. The effects of diltiazem 180 mg/day and propranolol 240 mg/day, alone and in combination, were compared with respect to symptomatic improvement and exercise performance in 15 patients with stable angina pectoris.

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Patients and methods

Patients with a history of stable exertional angina pectoris were considered for entry into the study. Patients were included if they had chest pain associated with >1 mm horizontal or down sloping ST segment depression at 0·08 s after the J point on treadmill exercise testing. Those who had a history of congestive cardiac failure, conduction abnormalities on the resting electrocardiogram, unstable angina pectoris, or myocardial infarction in the three months preceding the study or in whom the withdrawal of antianginal drugs was considered to be inadvisable were excluded from the study. Patients were also excluded if they had evidence of notable hepatic, renal, metabolic, or pulmonary disease.

We studied 15 men (mean (range) age 57·3 (50–67) years). Four patients had a history of transmural myocardial infarction. Coronary arteriography was performed in 14 patients. In reporting the coronary arteriogram, stenoses of the luminal diameter ≥75% were considered to be significant. Three patients had stenoses in three major vessels, five had two vessel disease, and six single vessel disease. At left ventricular angiography all patients had an ejection fraction of >50% and a left ventricular end diastolic pressure of <16 mm Hg.

TRIAL PROTOCOL

In this study we used a double blind placebo controlled crossover trial consisting of four periods of treatment each lasting four weeks. The four regimens were placebo, diltiazem 60 mg three times a day, propranolol 80 mg three times a day, and diltiazem 60 mg combined with propranolol 80 mg three times a day. All patients received all treatments, the order of administration being determined by a balanced latin square. The trial was double blind, and at all times the treatments were visually identical. Each period of treatment was separated by one week during which all antianginal drugs except for sublingual glyceryl trinitrate were withdrawn. At the end of a one week run in period, during which only sublingual glyceryl trinitrate was given, when required, a symptom limited treadmill exercise test was performed. Thereafter exercise tests were performed during the final week of each period of treatment and at the end of each week that separated the periods of treatment. All the treadmill exercise tests were performed according to the Bruce protocol at the same time of day for each patient.[10] All exercise tests were symptom limited, the end points being severe dyspnoea, severe chest pain, or intolerable fatigue. Heart rate, blood pressure, and a modified 12 lead electrocardiogram were recorded at rest, at the end of each stage of the Bruce protocol, at peak exercise, and at intervals of two minutes during the recovery period. We were thus able to obtain exercise duration, time to 1 mm ST segment depression, and time to the onset of angina. The electrocardiograms at each stage were analysed by calculating the sum of the number of millimetres of significant ST segment depression (>1 mm) in each lead at each stage. Rate pressure product was calculated as the product of systolic blood pressure and heart rate.

A subjective assessment of the efficacy of treatment during each period was obtained by patients maintaining a detailed diary of the frequency of anginal attacks and the number of sublingual tablets of glyceryl trinitrate consumed. Sublingual glyceryl trinitrate was not permitted prophylactically.

STATISTICAL ANALYSIS

Statistical analysis was performed with analysis of variance of repeated measurements.[11] If a significant result was found, Student's paired *t* test was used for comparison between two treatments. All values were expressed as mean (SEM).

Results

SUBJECTIVE DATA

Although the total number of anginal episodes a week was reduced from 7(3) during treatment with placebo to 3(1) during treatment with diltiazem, 2(1) during treatment with propranolol, and 1(1) during combination treatment, this reduction was not significant. Similarly, glyceryl trinitrate consumption per week was not significantly decreased, though it was reduced from 6(3) during treatment with placebo to 3(1) during treatment with diltiazem, 1(1) during treatment with propranolol, and 1(1) during combination treatment.

OBJECTIVE DATA

Combination treatment with diltiazem and propranolol produced significant increases in the duration of exercise, time to the onset of angina, and time to 1 mm ST depression compared with placebo (Table 1). Duration of exercise increased from 371(39) s during treatment with placebo to 437(28) s during combination treatment ($p<0·02$). Duration of exercise improved significantly compared with placebo during propranolol treatment, but no significant change occurred during diltiazem treatment. Time until the onset of angina or until the stopping of exercise if angina did not develop increased from 293(32) s with placebo to 421(34) s ($p<0·001$) during treatment with diltiazem and propranolol combined. A similar significant increase of the order of 40% occurred in the duration of exercise to the onset of 1 mm ST segment depression after com-

Table 1 *Mean (SEM) total duration of exercise, time to onset of angina, and time to 1 mm ST segment depression in 15 patients receiving four different treatments*

	Placebo	*Diltiazem*	*Propranolol*	*Diltiazem and propranolol*
Duration of exercise (s)	371(39)	396(32)	412(29)*	437(28)**
Time to angina (s)	293(32)	347(38)***	350(30)***	421(34)****
Time to 1 mm ST depression (s)	292(37)	332(37)*	387(37)***	403(34)***

Significance of difference when compared with placebo: *$p<0{\cdot}05$; **$p<0{\cdot}02$; ***$p<0{\cdot}01$; ****$p<0{\cdot}001$.

Table 2 *Mean (SEM) rate-pressure product at rest and peak exercise in 15 patients receiving four different treatments*

	Placebo	*Diltiazem*	*Propranolol*	*Diltiazem and propranolol*
Rate-pressure product (mm Hg beat/min $\times 10^{-3}$) at:				
Rest	12·1(0·6)	10·8(0·9)	7·5(0·4)*	6·3(0·6)*
Peak exercise	23·7(1·5)	23·0(1·1)	16·4(0·6)*	14·0(0·8)*

Significance of difference when compared with placebo: *$p<0{\cdot}001$.

bination treatment compared with placebo.

Treatment with either diltiazem or propranolol alone produced significant increases in time to onset of angina and 1 mm ST depression, but these increases were not as pronounced as those occurring during combination treatment. Angina pectoris occurred during the treadmill exercise test in all patients when receiving placebo. Angina was absent in seven patients when receiving combination treatment ($p<0{\cdot}05$ compared with placebo; McNemar's test). Angina pectoris was absent in four patients when receiving diltiazem and two when receiving propranolol.

Reflecting reduced electrocardiographic evidence of ischaemia, the sum of ST segment depression at peak exercise decreased significantly from 6·7(0·9) mm during placebo treatment to 3·9(0·7) mm during combination treatment ($p<0{\cdot}01$). A significant reduction, to 5·4(0·9) mm ($p<0{\cdot}05$), also occurred during propranolol treatment, but treatment with diltiazem produced only a non-significant reduction to 6·1(0·9) mm. Rate pressure product fell during combination treatment by about 50% when compared with placebo (Table 2). Similarly, at peak exercise rate, pressure product decreased from 23·7(1·5) mm Hg beats/min 10^{-3} with placebo to 14·0(0·8) mm Hg beats/min 10^{-3} during combination treatment ($p<0{\cdot}001$). Propranolol alone, but not diltiazem, produced significant reductions in rate pressure product at rest and during exercise.

ADVERSE EFFECTS

No important adverse effects were noted in patients taking placebo, diltiazem, or propranolol. Adverse effects were noted in two patients who received a combination of diltiazem and propranolol. One, who had a previous anterior myocardial infarct and a dyskinetic anterolateral segment at left ventricular angiography, developed dyspnoea after starting combination treatment. This was associated with a sinus bradycardia of 45 beats/minute and resolved on stopping treatment. The second patient developed fatigue associated with a sinus bradycardia of 36 beats/minute. This adverse effect responded to a reduction by one tablet in the dose of each drug: diltiazem dosage was reduced to 120 mg/day and propranolol to 160 mg/day.

Discussion

The beneficial effect in angina pectoris of combined diltiazem and propranolol treatment has been shown in this study by the objective evidence of increased duration of exercise, increased time to the onset of angina, and increased time to 1 mm ST segment depression. This was coupled with reduced electrocardiographic evidence of ischaemia compared with placebo. Although there was a trend towards subjective improvement as evidenced by the frequency of angina and the consumption of glyceryl trinitrate, this change was not significant.

The objective evidence of improvement supports similar studies showing that, when calcium channel blocking agents such as nifedipine or verapamil are combined with a beta blocker, combination treatment is more effecive that either a calcium channel blocker or a beta blocker used alone.[4 5] Diltiazem alone has been shown to improve exercise tolerance in angina pectoris, and this effect appears to be more pronounced with increasing dosages.[6 7 12] In this study we used diltiazem in a dose of 180 mg/day, at which dose it did not produce a significant improvement in duration of exercise or electrocardiographic evidence of ischaemia. Some dose titration studies have shown little benefit in exercise tolerance when diltiazem is used in doses of less than 240 mg/day.[6 13] In a recent study similar in design to ours diltiazem in a dose of 360 mg/day appeared to be as effective or more effective than combined diltiazem (360 mg/day) and propranolol (240 mg/day).[14] In that study, combination treatment when compared with diltiazem alone, although not prolonging exercise time, did reduce electrocardiographic evidence of ischaemia. Patients in the study on combination treatment were often limited by fatigue. Similarly, in our study, although time to onset of angina was increased by 40%, the duration of exercise was increased by only 18% compared with placebo as many patients, although not experiencing angina, were limited by fatigue. This was probably due to an appreciable reduction in peak heart rate. In the study of Hung *et al* four of 12 patients receiving combination treatment experienced side effects requiring a reduction in dosage compared with two of 15 patients in our study.

The beneficial action of calcium channel blockers in effort induced angina is multifactorial.[1] They may increase myocardial oxygen supply by increasing coronary blood flow. They may also reduce myocardial oxygen demand by reducing afterload by decreasing peripheral vascular resistance, and in some cases reducing contractility and heart rate. Combination treatment with diltiazem and propranolol produced significant reductions of the order of 40% in rate pressure product both at rest and peak exercise. Rate pressure product during exercise has been shown to correlate well with myocardial oxygen consumption.[15] Thus combination treatment appears to achieve its beneficial effect through a reduction in myocardial oxygen demand. Propranolol alone also significantly reduced rate pressure product both at rest and during exercise but not to the same extent as combination treatment. Diltiazem alone did not significantly alter rate pressure product, and this may well account for its failure to improve duration of exercise and reduce electrocardiographic evidence of ischaemia. Nevertheless, it increased time to the onset of angina and time to 1 mm ST depression. This beneficial effect may have been related to increased myocardial oxygen supply as diltiazem has been shown to increase coronary sinus blood flow in man.[16]

This study objectively shows the superior value of diltiazem and propranolol combined in effort related angina compared with either drug used alone. The beneficial effects of combination treatment appear to be mediated by a reduction in myocardial oxygen consumption. Caution in using combined diltiazem and propranolol treatment is, however, indicated by this and other studies, and careful titration of diltiazem dosage should be carried out to minimise side effects.

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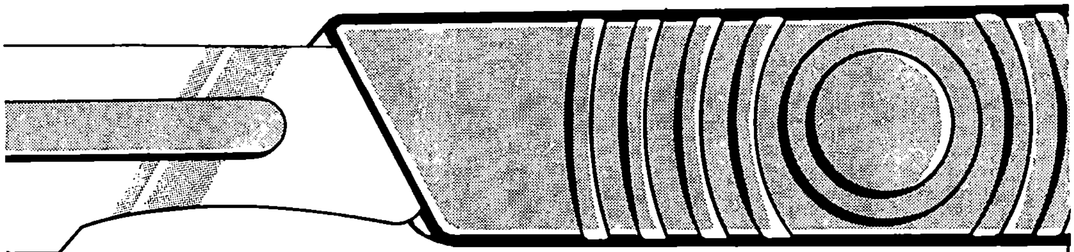

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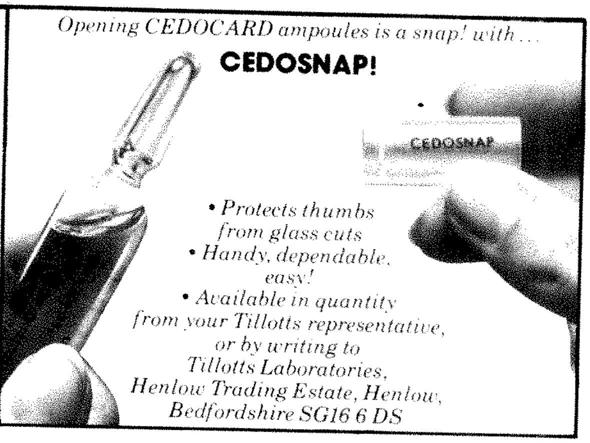

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Effects of combined alpha and beta adrenoceptor blockade in patients with angina pectoris

A double blind study comparing labetalol with placebo

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SUMMARY The effects of a combined alpha and beta receptor antagonist, labetalol, were investigated in 10 patients with chronic stable angina pectoris. The optimal dose was determined during an initial dose titration study when the patients were treated with 200 mg, 400 mg, and 600 mg (six patients) of labetalol a day. The effective dose was then compared with placebo in a double blind randomised study. The effects of the drug were monitored with angina diaries, treadmill exercise testing, and 48 hour ambulatory electrocardiographic ST segment monitoring. Plasma labetalol concentrations were measured during each treatment period. The mean effective antianginal dose of labetalol was 480 (SD 140) mg/day given by mouth twice a day. There was a dose related reduction in daytime and nocturnal heart rate, the frequency of pain was significantly reduced by 41%, and exercise duration was significantly increased by 44% with labetalol when compared with placebo. The frequency and duration of the episodes of ST segment depression were significantly reduced by 56% and 73% respectively with labetalol. Adverse effects resulted in a reduction of the dose of labetalol in two patients. Thus labetalol is an effective agent in the treatment of angina pectoris.

Although beta adrenoceptor antagonists have become established in the treatment of patients with exertional angina pectoris,[1] their role in treating angina at rest remains controversial since myocardial ischaemia in these circumstances is often thought to be secondary to reduction in myocardial blood flow, possibly as a result of coronary spasm.[2 3] As coronary vascular tone is mediated via both alpha (vasoconstrictive) and beta (vasodilative) adrenergic nerve endings[4] pure beta adrenergic blockade may increase coronary tone not only directly but also indirectly by permitting unopposed alpha vasoconstrictor action. It seemed reasonable therefore to consider alpha blocking agents in the treatment of angina pectoris.[5 6] Pure alpha blockers, however, were found to be unpredictable in patients with myocardial ischaemia because they tend to cause tachycardia.[7 8] A safer and more predictable formulation was obtained by combining an alpha blocker with a beta blocker, which theoretically avoids the drawback of tachycardia and the potential risks of exacerbating coronary spasm.[9]

Labetalol, 5-(1-hydroxy-2-[(1-methyl-3 phenylpropyl) amino] ethyl) salicylamide, has both beta and alpha receptor blocking properties.[9–13] It has nonselective beta blocking actions, with competitive antagonism of both beta$_1$ (cardiac) and beta$_2$ (bronchial and vascular) receptors with beta$_1$ receptor blockade somewhat more prominent than beta$_2$ blockade.[9] Labetalol has partial beta$_2$ agonist activity, some direct vasodilative activity, and membrane stabilising activity and is lipid soluble and excreted through the kidneys (50%) after conjugation in the liver.[9] It is currently used as an antihypertensive agent in all grades of hypertension.[14–16] A few studies have shown the effectiveness of labetalol in hypertension and angina.[5 6 17–20]

This study was designed to assess the effects of labetalol in patients with angina pectoris using a double blind placebo controlled technique. Previous dose titration was carried out to determine the optimum dosage for each patient. In addition to the measurements of angina frequency and exercise capacity, we objectively assessed the magnitude, frequency, and duration of myocardial ischaemia during

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each treatment phase by means of ambulatory electrocardiographic ST segment monitoring.

Patients and methods

Ten patients (eight men, two women) aged 42 to 72 years with at least a three month history of chronic stable angina pectoris were studied. Eight patients had angiographically confirmed obstructive coronary artery disease and two a well documented history of myocardial infarction. Before the study all patients had been shown to develop chest pain and significant ST segment depression during treadmill exercise testing and ambulatory electrocardiographic monitoring. No patients had episodes of ST segment elevation. All patients had previously been treated with beta adrenoceptor antagonists.

STUDY PHASES

The study was divided into two phases.

Dose titration—Each patient was treated with labetalol twice daily. The total daily dose was 200 mg for two weeks and 400 mg for two weeks in all the patients and 600 mg for two weeks in six patients. Patients kept angina diaries and had exercise testing and 48 hour ambulatory electrocardiographic ST segment monitoring performed at the end of each two week treatment period.

Double blind comparison—The optimum effective dose of labetalol for each patient was determined during the dose titration phase. The patients were then randomly allocated to treatment with this dose of labetalol for two weeks and placebo for two weeks in a double blind crossover manner. Assessment with angina diaries, exercise testing, ambulatory ST segment monitoring, and blood concentrations of labetalol was performed at the end of each treatment period.

ANGINA DIARIES

A detailed record of the time and frequency of chest pain and activity at the time of pain was kept throughout both phases of the study.

EXERCISE TESTING

All patients underwent incremental treadmill exercise testing according to the modified Bruce protocol[21] at the end of each two week treatment period. Maximal symptom limited exercise tests were performed in which the 12 lead electrocardiogram was recorded at the end of each minute. Significant ST segment depression was defined as a depression of ≥ 1 mm in magnitude occurring 0·08 s after the J point which persisted for at least three consecutive beats.

AMBULATORY MONITORING

Forty eight hour ambulatory electrocardiographic monitoring was performed using a frequency modulated recorder (Oxford Medilog II, frequency response 0·05–40 Hz). A two channel recording was obtained with bipolar leads CM5 and modified lead II. The magnetic tapes were read visually at 60 times normal speed (Oxford Medilog MA20 analyser), and the number, duration, and magnitude of ST segment changes were noted. Significant ST segment depression was defined as depression of ≥ 1mm in magnitude occurring 0·08 s after the J point and persisting for at least one minute. An hourly heart rate trend was also obtained during each monitoring period. Patients underwent their normal daily activities during the 48 hour period of ambulatory monitoring in order to assess the effect of treatment under similar circumstances. The daytime heart rate was determined at the beginning of the exercise tests and the mean nocturnal heart rate calculated from the average of the hourly heart rates between 2400 and 0600 obtained during ambulatory monitoring.

LABETALOL ASSAY

The serum labetalol concentration was measured at the end of each two week treatment period throughout the dose titration and double blind phases of the study by a high performance liquid chromatography assay. This was used to assess patient compliance only since the samples were obtained 2–18 hours after the last dose of the drug.

STATISTICAL ANALYSIS

Results are expressed as mean and standard deviation. Discrete data were analysed using the Wilcoxon signed rank test for paired observations and was restricted to the double blind phase of the study.

Results

DOSE TITRATION

All patients were given the 200 mg/day and the 400 mg/day doses of labetalol. Six patients did not become asymptomatic and were therefore given labetalol 600 mg/day. The dose allocation for the second phase of the study was ascertained from the history and ambulatory monitoring data.

Heart rate and blood pressure—Table 1 shows the effect of increasing doses of labetalol on the resting heart rate, blood pressure, and rate pressure product. There was a dose related reduction in the resting daytime heart rate and in both the systolic and diastolic arterial blood pressure (Table 1, Figure).

Angina frequency—Table 2 shows the frequency of chest pain associated with ST segment depression during the 48 hour ambulatory monitoring period and

Table 1 *Effect of labetalol on the resting heart rate, blood pressure, and rate-pressure product during the dose titration and double blind studies. Results are mean (standard deviation)*

	Heart rate (beats/min)		*Resting blood pressure (mm Hg)*		*Rate-pressure product*
	Daytime	*Nocturnal*	*Systolic*	*Diastolic*	
			Dose titration study		
Labetalol (mg)					
200	76 (12)	65 (8)	130 (17)	80 (8)	9900 (2370)
400	70 (15)	64 (11)	119 (17)	81 (8)	8470 (2510)
600 (n=6)	64 (12)	61 (9)	116 (12)	76 (10)	7500 (2220)
			Double blind study		
Placebo	83 (10)	69 (12)	141 (21)	94 (13)	11350 (2380)
Labetalol (480 (140) mg)	69 (13)**	64 (10)*	110 (15)**	75 (10)**	7900 (1820)**

$^*p<0.05$, $^{**}p<0.01$.

during the last seven days of each treatment period. All patients continued to have angina with labetalol 200 mg a day. Three patients became free of pain with 400 mg/day, although two of these had episodes of painless ST segment depression during monitoring. One patient had a systolic blood pressure of 95 mm Hg with labetalol 400 mg/day but remained asymptomatic. Another patient was pain free with 400 mg/day but had postural hypotension. Three of the six patients treated with 600 mg/day had no pain during the last seven days or during the last 48 hour monitoring period, and the other three patients had a greatly decreased frequency of pain.

Exercise testing—Table 3 shows the duration of exercise, heart rate, and systolic blood pressure at the time of development of 1 mm planar or downsloping ST segment depression. The duration of exercise to 1 mm ST segment depression was increased in eight of the 10 patients with 400 mg/day, and the total exercise duration was increased in nine. With 600 mg/day three of the six patients showed further improvement in total exercise capacity and duration of exercise to 1 mm ST depression. The other three patients exercised to the same workload as with the 400 mg/day dose. A stepwise increase in beta blockade was evident with increasing doses of labetalol. The mean heart rate after three minutes of exercise was 100 (15) beats/min with 200 mg/day, 95 (12) beats/min with 400 mg/day, and 91 (13) beats/min with 600 mg/day. Both the heart rate and systolic blood pressure at the onset of 1 mm ST depression and at the end of the test tended to be lower with the higher doses of labetalol even though the workload achieved was greater (Table 3).

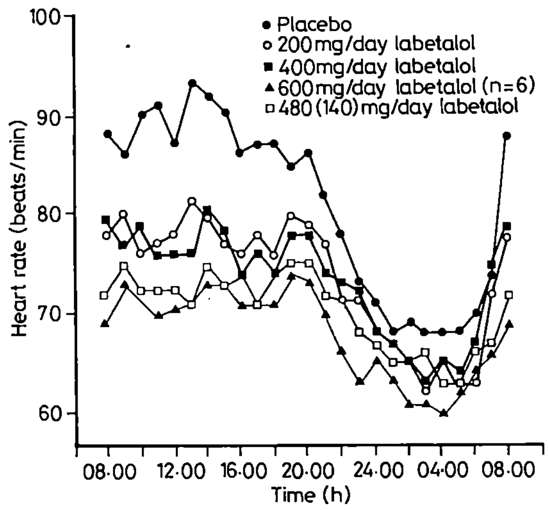

Figure *Hourly heart rate changes during 24 hours of ambulatory monitoring with labetalol during the dose titration and double blind phases of the study.*

Ambulatory ST segment monitoring—Table 2 shows the number, duration, and magnitude of episodes of ST segment depression. Compared with labetalol 200 mg/day, 400 mg/day produced a reduction in the number and duration of episodes of ST segment depression in four patients. With 600 mg/day all six patients showed an improvement in the frequency or the duration of ischaemia.

Plasma labetalol concentration—All patients complied with drug treatment throughout the dose titration phase (Table 4).

DOUBLE BLIND COMPARISON

The optimum dose for the double blind phase of the study was 200 mg/day in one patient, 400 mg/day in four, and 600 mg/day in five (mean 480 (140) mg/day). One patient developed severe and frequent chest pain during the placebo period, which was limited to five days.

Heart rate and blood pressure—The mean daytime resting heart rate, the mean nocturnal heart rate, and the mean systolic and diastolic arterial blood pressures were lower with labetalol than with placebo (Table 1). The daytime heart rate was lowered by a mean of 17% ($p<0.01$), whereas the mean nocturnal heart rate was reduced by 7% ($p<0.05$) with labetalol (Figure).

Table 2 *Frequency, magnitude, and duration of episodes of ST segment depression during each 24 hour period of ambulatory monitoring and the frequency of pain during the dose titration and double blind phases of the study. Results are mean (standard deviation)*

	ST segment depression			*No of painful episodes of ST depression*	*No of episodes of pain/week*
	No of episodes	*Duration of episodes (min)*	*Mean maximum magnitude (mm)*		
			Dose titration study		
Labetalol (mg)					
200	4·3 (3·2)	67 (70)	1·8 (1·1)	1·2 (1·3)	13 (12)
400	4·7 (3·9)	72 (65)	2·0 (1·2)	1·4 (1·4)	8 (9)
600 (n=6)	2·3 (1·4)	36 (26)	2·3 (0·5)	0·2 (0·3)	2 (3)
			Double blind study		
Placebo	3·4 (2·6)	80 (87)	1·9 (1·3)	1·1 (1·0)	10 (9)
Labetalol (480 (140) mg)	1·5 (2·2)**	22 (50)**	1·9 (1·4) (NS)	0·1 (0·3)*	5·9 (8·8)**

*$p<0{\cdot}05$, **$p<0{\cdot}01$, NS, not significant.

Angina frequency—When compared with placebo, labetalol at a mean dose of 480 (140) mg/day reduced the angina attack frequency by 41% ($p<0{\cdot}01$). Chest pain was completely abolished in three patients. The frequency of chest pain was reduced in another five patients. One patient experienced the same frequency of pain during both the active treatment and placebo periods, while one patient had one more episode of pain with labetalol compared with placebo (Table 2).

Exercise testing—The duration of exercise before the development of ST segment depression was increased by 44% ($p<0{\cdot}01$) after labetalol compared with placebo. The total duration of exercise was increased by 29% ($p<0{\cdot}01$), and all patients showed an improvement in exercise capacity (Table 3).

Evidence of beta blockade was not only observed at rest, when the heart rate and blood pressure values were lower (Table 1), but was evident at each stage of exercise. After three minutes of exercise, mean heart rate had increased from 83 (10) beats/min to 95 (12) beats/min with placebo and from 69 (13) beats/min to 80 (12) beats/min with labetalol. After six minutes' exercise, the heart rate had increased to 112 (14) beats/min ($n=8$) with placebo and 93 (13) beats/min with labetalol. The mean heart rate and systolic blood pressure at the onset of 1 mm ST segment depression and at the termination of exercise were significantly lower during labetalol treatment (Table 3) ($p<0{\cdot}01$). The rate of increase in heart rate was not significantly different after three minutes of exercise with labetalol (11 (6) beats/min) compared with placebo (12 (4) beats/min). Nevertheless, the rate of increase in heart rate was significantly lower at six minutes of exercise in the eight patients who reached this level (increase of 32 (6) beats/min) with placebo and 25 (3) beats/min with labetalol ($p<0{\cdot}05$)).

Ambulatory ST segment monitoring—Treatment with labetalol (480 (140) mg/day) abolished all episodes of ST segment depression in five patients and significantly reduced the frequency and duration of

Table 3 *Duration of exercise and haemodynamics after treadmill exercise to 1 mm ST segment depression and at the termination of the test during the dose titration and double blind phases of the study. Results are mean (standard deviation)*

	Haemodynamics to 1 mm ST depression				*Haemodynamics at termination*			
	Exercise duration (min)	*Heart rate (beats/min)*	*Systolic blood pressure (mm Hg)*	*Rate-pressure product*	*Exercise duration (min)*	*Heart rate (beats/min)*	*Systolic blood pressure (mm Hg)*	*Rate-pressure product*
				Dose titration study				
Labetalol (mg)								
200	5·1 (1·7)	110 (19)	149 (26)	16720 (5040)	6·4 (2·2)	122 (21)	152 (28)	18820 (5900)
400	6·5 (1·7)	110 (16)	136 (16)	15090 (3770)	8·1 (1·9)	117 (20)	138 (24)	16570 (5420)
600 (n=6)	7·2 (1·3)	107 (15)	138 (27)	14920 (4450)	8·7 (1·5)	115 (22)	138 (36)	16380 (6325)
				Double blind study				
Placebo	5·4 (2·0)	121 (12)	166 (34)	20440 (5739)	6·8 (1·7)	131 (15)	177 (40)	23560 (7410)
Labetalol (480 (140) mg)	7·8 (1·9)**	110 (15)**	133 (20)**	14810 (3590)**	8·5 (1·6)**	114 (15)**	137 (22)**	15710 (4180)**

**$p<0{\cdot}01$.

Table 4 *Mean (SD) plasma labetatol concentration during the dose titration and double blind phases of the study*

Dose	*Plasma labetalol concentration (μg/l)*
Dose titration study	
Labetalol (mg)	
200	40 (17)
400	98 (42)
600 (n=6)	197 (110)
Double blind study	
Placebo	0
Labetalol (480 (140) mg)	187 (167)

both painful and painless episodes of ST segment depression in the other five when compared with placebo ($p<0{\cdot}01$) (Table 2). The maximum magnitude of the episodes of ST segment depression was not significantly altered with labetalol, although the number of these episodes was lower (Table 2).

Plasma labetalol concentrations—All patients complied with the double blind phase of the trial, and Table 4 shows the serum labetalol concentrations.

Adverse effects—Five patients complained of leg fatigue and three intermittent claudication during labetalol treatment. One patient had episodes of postural hypotension with labetalol 400 mg/day and was therefore randomised to receive 200 mg/day. One patient complained of increased dyspnoea on exertion with 400 mg/day compared with the lower dose. One patient developed an increase in the frequency of dreams and one had difficulty in micturition with labetalol treatment.

Discussion

Although beta adrenoceptor antagonists have become a mainstay in the treatment of angina pectoris, these agents are also known to increase the peripheral vascular resistance and left ventricular end diastolic pressure, which causes increases in myocardial oxygen demand.[4] Furthermore, blockade of the vasodilative beta receptors on the coronary arteries would result in the unmasking of alpha mediated vasoconstrictor activity[4 22–24] and hence reduce coronary blood flow.[13 25] Alpha adrenoceptor blocking agents increase coronary blood flow and reduce coronary[12 24 26] and peripheral vascular resistance and cause a fall in arterial blood pressure.[9] Labetalol is a unique compound which possesses both non-selective beta receptor and alpha$_1$ receptor blocking properties. It therefore produces all the beneficial effects of pure alpha blockers on the coronary and peripheral vasculature, but the tachycardia is blocked by beta receptor blockade. In isolated tissue preparation, labetalol is 4–8 times more potent in blocking beta receptors than alpha receptors.[9] Patients with hypertension and angina pectoris have shown improvement in exercise capacity at a dose of labetalol which has ranged from 300 to 1600 mg/day.[5 6 16–20] In this study we performed dose titration and found that the effective antianginal action of labetalol was evident at a mean daily dose of 480 (140) mg/day, a dose considerably lower than that in the hypertensive group of patients. The reduction in daytime heart rate of the patients in this study was comparable to the reduction seen in the hypertensive patients,[6] although the reduction in arterial blood pressure in our patients was less pronounced. It is likely, therefore, that normotensive patients with myocardial ischaemia require lower doses of labetalol for therapeutic effect than patients who have hypertension.

All patients in this study had a history of chronic stable exertional angina pectoris. None had a history of frequent rest pain, and no episodes of nocturnal ST segment change were noted. Thus the theoretical benefit of coronary vasodilatation with an alpha receptor antagonist could not be established convincingly in this group of patients. Comparison with a pure beta adrenoceptor antagonist, particularly in patients with angina at rest, is necessary to show any increased benefit with a combined alpha and beta receptor antagonist such as labetalol.

During exercise testing the heart rate, blood pressure, and the rate-pressure product were all lower with labetalol than with placebo even at the lowest dose of 200 mg/day. Nevertheless, a significant increase in the duration of exercise was noted only at a higher dose of 400 mg/day and a significant antianginal effect was evident with a mean dose of 480 (140) mg/day of labetalol. These findings of a significant haemodynamic effect at relatively low doses and antianginal action at a relatively higher dose have also been reported in patients who have angina and hypertension.[6]

Although the heart rate and blood pressure at all stages of exercise were lower with labetalol, a reduction in the rate of increase of heart rate was observed only after six minutes of exercise. The effect on arterial blood pressure at different stages of exercise is difficult to determine in this study since a few patients had a fall in blood pressure towards the later stages of exercise when they were receiving placebo. There was no significant difference between the magnitude of the increase in systolic blood pressure at the termination of the exercise test when compared with placebo, although the patients had exercised longer at the higher doses of labetalol. These results contrast with the findings in patients with hypertension.[6]

In this study two important aspects of the use of labetalol in normotensive patients with angina pectoris were investigated for the first time. Firstly, the effective dose of labetalol was determined in each individual by graded dose titration, and the optimum dose was then compared with placebo in a double blind study. Secondly, the frequency of myocardial ischaemic episodes was determined both subjectively (angina diaries) and objectively by ambulatory ST segment monitoring. This showed that the frequency and duration of both painful and painless episodes of reversible ST segment depression were reduced by labetalol at a mean dose of 480 (140) mg/day. Care was taken to ensure that ST segment monitoring was performed during days when the patients underwent their normal daily activities. Therefore, not only was the effectiveness of labetalol in increasing exercise capacity demonstrated during conventional exercise tests, but there was also objective evidence of improvement in both symptomatic and asymptomatic episodes of myocardial ischaemia. This study shows that labetalol is an effective antianginal agent in patients with obstructive coronary artery disease. It has certain theoretical advantages over conventional beta adrenoceptor antagonists, and the clinical relevance of these needs to be investigated in future comparative studies.

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Oral labetalol in the management of stable angina pectoris in normotensive patients

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SUMMARY The efficacy of labetalol, an alpha and beta receptor antagonist, was evaluated in 12 normotensive patients with stable angina pectoris in a single blind dose ranging study. After a two week period of placebo treatment, labetalol was given in doses of 100, 150, 200, and 300 mg twice daily, each for two weeks. Frequency of angina attacks decreased from 9·4 (SEM 2·3)/week in the control period to 7·3 (2·8), 5·2 (2·6), 3·8 (1·8), and 3·3 (1·9)/week in the four successive treatment periods. In the same periods the number of glyceryl trinitrate tablets consumed decreased from 7·0 (2·6)/week to 5·8 (3·3), 3·9 (2·9), 2·7 (1·8), and 2·6 (2·1)/week. Maximal symptom limited treadmill exercise tests were performed three and 12 hours after dosage at each dose. Exercise tolerance (expressed as seconds of the Bruce protocol) increased from 266 (44) with placebo to 306 (44), 369 (50), 396 (48), and 413 (51) in the four treatment periods. This improvement was accompanied by a significant blunting of the heart rate and blood presssure responses to exercise. Trough point exercise tolerance did not differ significantly from that at three hours after dosage.

Thus labetalol is effective as an antianginal agent at doses of 150–300 mg twice daily and is well tolerated by the normotensive patient with angina.

The value of beta receptor antagonists in the management of patients with stable angina pectoris is well established.[1 2] The benefits of beta blockade are, however, achieved at the expense of a decrease in cardiac output and an increase in peripheral vascular resistance.[3] These haemodynamic effects may be important in the aetiology of the not infrequent side effects of beta blockade: cold hands and feet and fatigue. Labetalol is an agent which possesses both alpha and beta adrenoceptor antagonist properties.[4] Short term studies have shown a reduction in peripheral vascular resistance after its intravenous administration[3 5] and, compared with propranolol, less impairment of left ventricular haemodynamic performance.[3] In addition, in contrast to propranolol, labetalol produces a reduction in coronary vascular resistance.[5]

Labetalol's main role has been in the treatment of hypertension,[6–8] and in a preliminary report of labetalol treatment in patients with both hypertension and angina amelioration of anginal symptoms has been described.[9]

The object of this study was to assess the effects of labetalol in normotensive patients with stable angina pectoris, with reference to the control of anginal symptoms and effect on exercise tolerance.

Patients and methods

Thirteen patients (10 men and three women, mean age 59 (range 41–66) years) participated in the study. All had had clinically stable exercise induced angina pectoris for three months or longer. Table 1 summarises the patients' details. No patient had valvar heart disease, cardiac failure, obstructive airways disease, hypertension (resting diastolic blood pressure >100 mm Hg), diabetes, or renal or thyroid disease. All patients were limited on treadmill exercise testing by angina pectoris accompanied by horizontal or downsloping depression of the ST segment of ≥1·0 mm, persisting to 80 ms beyond the J point. Eleven patients had angiographically confirmed coronary disease, defined as >70% stenosis of at least one major vessel. The remaining two patients, who declined angiography, had typical angina and ST depression of

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Table 1 *Details of patients*

Case No	*Age (yr)/sex*	*Exercise limited by*	*Coronary arteriogram findings**
1	58/M	Angina	3 Vessel disease
2	51/F	Angina	2 Vessel disease
3	66/M	Angina	2 Vessel disease
4	61/F	Angina	2 Vessel disease
5	63/M	Angina	Not done
6	62/M	Angina	2 Vessel disease
7	64/M	Angina	Single vessel disease
8	64/M	Angina	2 Vessel disease
9	60/M	Angina	3 Vessel disease
10	41/F	Angina	3 Vessel disease
11	54/M	Angina	2 Vessel disease
12	64/M	Angina	2 Vessel disease
13	55/M	Angina	Not done

*Coronary artery disease (>70% stenosis of the vessel lumen).

$\geq$3 mm at peak exercise. Patients were entered into the study after informed written consent had been obtained.

DRUG DOSAGE AND ADMINISTRATION

The study was divided into five two week periods. After a single blind placebo control period, labetalol was given in twice daily doses for the following eight weeks. The labetalol dosage was increased at two weekly intervals. The total daily labetalol dosage for the four treatment periods was 200 mg, 300 mg, 400 mg, and 600 mg.

ANTI-ANGINAL ASSESSMENT

Patients kept diaries to record the frequency of angina attacks and glyceryl trinitrate consumption. At each visit supine and standing blood pressures were measured using a standard sphygmomanometer. Patients were asked if they had experienced any side effects but were not questioned about specific symptoms.

EXERCISE TESTING

Maximal symptom limited treadmill exercise tests were performed using the Bruce protocol before entry into the study and in the second week of the placebo period and each treatment period. In each of the two week periods exercise tests were performed three hours and 12 hours after dosage on separate days. The treadmill, the recording equipment, and the recording methods have been described previously.[10]

STATISTICAL METHODS

To assess drug efficacy, the frequency of angina attacks and glyceryl trinitrate consumption in the control period were compared with those during treatment with labetalol. Exercise tolerance during treatment was compared with that with the second placebo to minimise any learning or training effect. Two way analysis of variance[11] was done to test the null hypothesis. Where differences were detected at at least the 5% level, the Newman-Keuls test[12] was used to compare the different treatments. Results are expressed as mean (SEM) unless stated otherwise.

Results

Full data were obtained in 10 patients. One patient required a reduction in dosage because of mild heart failure. Two patients were withdrawn from the study, one because of "scalp tingling" while taking labetalol and one because of progressive worsening of his angina while taking placebo.

ANGINA ATTACK FREQUENCY

The frequency of angina attacks decreased in all of the 10 patients who completed the study (Fig. 1). The reduction, compared with the placebo period, was significant with total daily labetalol doses of 300 mg, 400 mg, and 600 mg ($p<0{\cdot}01$ for each of these). With 400 mg daily and 600 mg daily, patients had significantly less angina than with 200 mg daily ($p<0{\cdot}05$ and $p<0{\cdot}01$ respectively). With between 300 mg and 600 mg daily, there was a further minor reduction in the frequency of angina attacks, but this was not statistically significant.

GLYCERYL TRINITRATE CONSUMPTION

The reduction in nitrate consumption paralleled the reduction in angina attack frequency (Fig. 1). There was a significant reduction in nitrate tablet consumption with labetalol 300 mg daily ($p<0{\cdot}05$) and also with 400 mg daily ($p<0{\cdot}01$) and 600 mg daily ($p<0{\cdot}01$) compared with placebo. With 400 mg and 600 mg daily, fewer glyceryl trinitrate tablets were taken than with 200 mg daily ($p<0{\cdot}05$). The further reduction on increasing the total daily labetalol dose from 300 mg to 600 mg was not significant.

EXERCISE TOLERANCE

Fig. 2 and Table 2 show exercise tolerance three hours after drug administration (expressed as seconds of the Bruce protocol). Exercise time with placebo was the

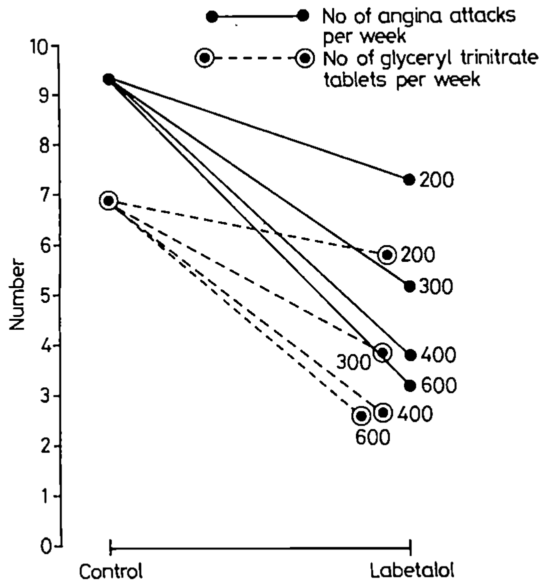

Fig. 1 *Relation of frequency of anginal attacks and glyceryl trinitrate consumption to doses of labetalol.*

same as that before entry without treatment. With labetalol 200 mg daily, exercise time was not significantly greater than with placebo. With labetalol 300 mg, 400 mg, and 600 mg daily, exercise tolerance was greater than with placebo (in each case p<0·01), and also greater than with labetalol 200 mg daily (p<0·05, p<0·01, and p<0·01 respectively). The exercise time with labetalol 600 mg daily (413 (50·6) s) was 55% greater than with placebo but was not significantly greater than with labetalol 300 mg daily. Exercise tolerance three hours after dosage was not significantly different from that 12 hours after dosage.

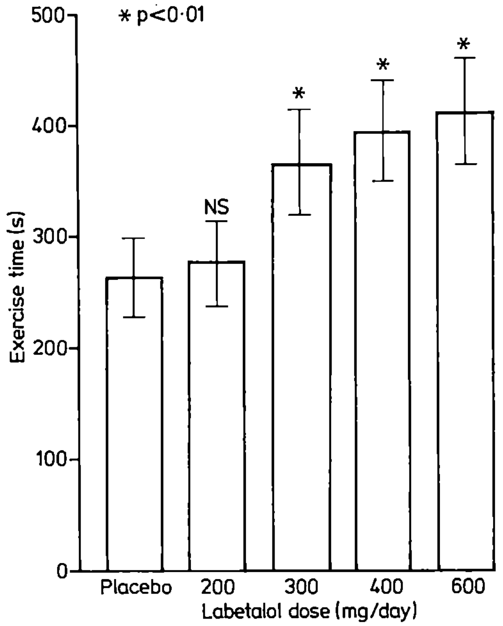

Fig. 2 *Relation of exercise tolerance to labetalol dosage. *p<0·01 vs placebo.*

BLOOD PRESSURE AND HEART RATE (TABLE 2)

The resting systolic blood pressure was significantly reduced by labetalol in a total daily dose of 200 mg (p<0·01). With 300 and 400 mg of labetalol daily, the resting systolic blood pressure was significantly lower than with placebo (p<0·01 at both dosages) but not lower than with 200 mg daily. With labetalol 600 mg daily the resting systolic pressure was significantly lower than with placebo (p<0·01) and also lower than with all the other dosages of labetalol (p<0·05). The

Table 2 *Rest and exercise data*

	Placebo periods			*Labetalol dose (mg/day)*			
	Control	*1st*	*2nd*	*200*	*300*	*400*	*600*
			Exercise data				
Heart rate at peak exercise (beats/min)	134 (8·3)	130 (7·1)	129 (7·0)	115 (4·9)	119 (6·1)	119 (4·7)	117 (5·2)
Peak exercise rate-presssure product (mm Hg min⁻¹)	23078 (2185)	22769 (2·74)	23943 (1712)	18654 (1270)*	18661 (1329)**	17809 (869)**	16790 (838)**
Heart rate at workload achieved in second placebo exercise test (beats/min)			129 (6·9)	113 (5·0)**	113 (5·4)**	109 (5·1)**	110 (4·2)**
Exercise tolerance (seconds of Bruce protocol)	238 (40·2)	251 (36·6)	266 (43·9)	306 (43·8)	369 (49·3)**	396 (47·7)**	413 (50·6)**
Maximum ST depression at peak exercise (mm)			2·0 (0·3)	1·6 (0·2)	1·6 (0·4)	1·8 (0·2)	1·7 (0·2)
			Data at rest				
Heart rate (beats/min)	77 (2·4)	73 (2·6)	75 (2·8)	69 (3·6)	68 (2·5)	66 (1·5)*	71 (2·1)
Blood pressure (mm Hg)							
Systolic	154 (7·1)	153 (7·6)	152 (7·4)	139 (7·3)**	131 (6·2)**	133 (6·7)**	121 (6·1)**
Diastolic	91 (2·6)	87 (3·6)	86 (2·9)	80 (4·2)*	79 (2·7)*	76 (3·5)**	75 (2·4)**

*p<0·05; **p<0·01 (significance of difference from placebo).

resting diastolic blood pressure was significantly lower with labetalol than with placebo, but there was not a significant difference in resting diastolic pressure between the different labetalol dosages.

There was a trend towards a reduction in resting heart rate which became significant at the 5% level with labetalol 400 mg daily. With 600 mg daily the resting heart rate was not significantly different from that with placebo.

The heart rate at peak exercise with labetalol was not significantly different from that with placebo. With labetalol, however, significantly higher workloads were achieved: When the heart rate at peak exercise with placebo was compared with that at the same workload with labetalol, a significant reduction was seen at all dosages ($p<0.01$ at each labetalol dosage).

The rate-pressure product at peak exercise was significantly reduced with all of the labetalol dosages (Table 2). The degree of reduction with 600 mg daily was not significantly different from that with 200 mg daily.

DEGREE OF ST SEGMENT CHANGE

Table 2 shows the maximum ST segment change seen on the 12 lead electrocardiogram at peak exercise at each dosage. There was a trend towards a reduction in the degree of ST segment depression, but this did not reach statistical significance.

EFFECT OF POSTURE ON SYSTOLIC BLOOD PRESSURE

Three hours after dosage with the highest labetalol dose there was a postural fall in systolic blood pressure in seven out of the 10 patients. The greatest fall was from 125 to 105 mm Hg. In the others the fall in systolic blood pressure ranged from 5 to 10 mm Hg. None of the patients had symptoms referable to postural hypotension.

SIDE EFFECTS AND WITHDRAWALS

One patient (case 3) was withdrawn after three days of treatment because of scalp tingling. One patient (case 6) developed dyspnoea on exertion while taking labetalol 200 mg daily. He did not have clinical signs of heart failure, but chest *x* ray films showed pulmonary venous congestion which was not previously present. Dosage reduction to 100 mg daily and the addition of a thiazide diuretic resulted in a pronounced symptomatic improvement. With placebo treatment he had experienced 14 attacks of angina a week and had consumed four glyceryl trinitrate tablets a week. With his final labetalol dosage he experienced only one attack of angina in a six week period. His exercise tolerance increased from 160 s in the control period to 221 s with his final dosage regimen, and his symptomatic improvement was maintained over a six month follow up period.

One patient (case 8) experienced progressive worsening of his angina while taking placebo and was withdrawn from the study before receiving labetalol. No patients complained of fatigue or cold extremities and none had symptoms referrable to postural hypotension.

Discussion

Labetalol is an agent with combined alpha and beta adrenoceptor antagonist properties.[4] It has a competitive antagonist action at both alpha and beta receptors,[4] and its beta blocking action is non-selective.[4] The intravenous administration of labetalol results in a fall in blood pressure and has a variable but generally minor effect on heart rate.[4 5 7 8] Peripheral vascular resistance has been shown to fall after its administration,[5 7] as has coronary vascular resistance.[5] Because of its haemodynamic effects its main role has been in the management of hypertension. In this context it has been shown to be effective, when given orally or intravenously,[6-8] and safe, even in the setting of acute myocardial infarction.[8]

The value of beta blockade in the management of angina pectoris is well established.[1 2] Pure beta blockade results in a reduction in resting heart rate and blood pressure and a blunting of the heart rate and blood pressure responses to exercise.[1 2] These actions result in a decreased myocardial oxygen requirement and are of benefit to the angina sufferer.[13] The benefits of beta blockade are, however, achieved at the expense of a decrease in cardiac output and a variable increase in peripheral vascular resistance[3 14]; these actions may be of importance in the production of the not infrequent side effects of fatigue and cold extremities.

Pure alpha blockade may be disadvantageous to patients with angina. Administration of the alpha receptor antagonist phentolamine results in a fall in peripheral vascular resistance and a fall in blood pressure[15] but any potential benefit, in terms of reduced myocardial oxygen requirement, is offset by the accompanying reflex tachycardia.[15 16] In some patients phentolamine may actually precipitate angina attacks.[15] Selective alpha$_1$ receptor blockade with prazosin has less tendency to produce reflex tachycardia, but exacerbation of anginal symptoms has also been described with the use of this agent.[16]

Alpha blockade alone clearly has disadvantages. There is some evidence, however, that the combination of alpha and beta blockade may be more effective than beta blockade alone in the treatment of angina.[17] In comparison with beta blockade alone the combination may provide additional benefit in terms of patient tolerance, since there is less depression of left ventricular function and less effect on peripheral vascular resistance than beta blockade.[3]

Labetalol is the only agent currently available that has combined alpha and beta adrenoceptor antagonist properties. It has been shown to ameliorate anginal symptoms in hypertensive patients with angina, but its effects in normotensive patients have not been previously evaluated in a controlled way. In this study, all the patients who received labetalol experienced an improvement in their anginal symptoms and an increase in their exercise capacity. These beneficial effects were statistically significant with the labetalol dose of 150 mg given twice daily. There was a trend towards further improvement with the administration of 200 mg and 300 mg twice daily, but compared with 150 mg twice daily this was not significant.

Labetalol caused a reduction in resting blood pressure and a minor reduction in resting heart rate. The latter effect was less than would be expected with agents such as propranolol or atenolol[1 2] and probably reflects the balance between the depressant effect of beta blockade on the sinus node and the tendency to reflex tachycardia in response to the alpha blockade mediated vasodilatation. The depression of resting heart rate was significant with 200 mg of labetalol twice daily but not with 300 mg twice daily. This probably reflects a response to the greater blood pressure lowering effect of the higher dosage.

Labetalol treatment was generally well tolerated; only one patient had to be withdrawn from the study in the active treatment period. This patient had the uncommon but well documented side effect of scalp tingling.[18] In view of labetalol's alpha blocking action, evidence of postural hypotension was sought; the greatest postural fall in systolic pressure was 20 mm Hg. No patient had symptoms that could be attributed to postural hypertension, and for the group as a whole the lying and standing systolic pressures were not significantly different.

In conclusion, labetalol is an effective antianginal agent that is well tolerated by normotensive patients and can be given in twice daily doses. Significant benefit was observed at a dose of 150 mg twice daily, and only minor improvement was achieved by further increases in dosage. One patient developed mild heart failure with the lowest dose, and it would seem prudent therefore to start treatment with 100 mg of labetalol twice daily and to titrate the dosage to suit the individual patient's needs. Labetalol has promise in the treatment of angina, as it may have advantages over beta blockade alone and merits further study.

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Transposition of the great arteries and narrowing of the aortic arch

Emphasis on right ventricular characteristics

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SUMMARY Of 279 patients with transposition of the great arteries, 14(5%) had narrowing of the aorta, including local coarctation (6), isthmus hypoplasia (6), isthmus atresia (1), and kinking of the aorta (1). There were six deaths in 10 surgically treated patients; in addition four patients died before operation. Two of the four survivors had a subpulmonary malalignment ventricular septal defect with angiocardiographic narrowing of the right ventricular outflow tract; two had evidence of redundant muscle tissue obstructing the right ventricular outflow tract. Necropsy showed the presence of anatomical right ventricular outflow tract or inflow tract obstruction or both in all 10 cases. Outflow tract obstruction was represented by anterior displacement of the infundibular septum and ventriculoinfundibular fold (in hearts with a subpulmonary malalignment ventricular septal defect) or by redundant muscle tissue; inflow tract obstruction was represented by hypoplasia of the tricuspid valve.

It is concluded that the combination of transposition of the great arteries and narrowing of the aorta is always accompanied by right ventricular outflow or inflow tract obstruction or both; the right ventricular abnormalities are probably responsible for the presence of the aortic arch anomalies by reducing aortic flow during morphogenesis. Successful surgical treatment of this complex anomaly is feasible in selected cases.

About one half of all cases of transposition are "simple," the second half being complicated by other anomalies.[1] The two commonest associated abnormalities in transposition are ventricular septal defect and left ventricular outflow tract obstruction, occurring separately or together. The incidence of a complicating obstruction of the aortic arch has been estimated to range between 4·6% and 10%.[2 3] More recently, complete transposition of the great arteries with ventricular septal defect and coarctation or atresia of the aortic arch has been described as a separate anatomicoclinical entity which includes inlet or outlet right ventricular obstruction.[4]

The present study was carried out to define right ventricular characteristics in patients with transposition of the great arteries and obstruction of the aortic arch.

Patients and methods

Two hundred and seventy nine patients with complete transposition of the great arteries were referred to the Leiden University Hospital between 1960 and 1982. Fourteen (5%) of these patients proved to have a complicating aortic arch obstruction. Four patients died before operation and six died after a Senning procedure, a Hanlon operation, banding of the pulmonary artery, coarctation resection, or a combination of these procedures. With one exception, the patients died before 1975; the four survivors were operated on more recently.

The angiograms and heart specimens were studied with special attention to the morphology of the right

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Table 1 *Clinical data of patients who underwent successful surgery*

Case No	*Aortic arch anomaly*	*Right ventricle*		*Ventricular septal defect*	*Surgical interventions*
		Outflow tract	*Inflow tract*		
1	COA	Anterior displacement of IS and prominent VIF	—	Subpulmonary malalignment	Blalock-Hanlon and banding (aged 1 mnth), repair of coarctation (aged 12 yrs), debanding; VSD closed; arterial switch (aged 12½ yrs), closure of residual VSD (aged 12½ yrs)
2	TH	Anterior displacement of IS and prominent VIF	—	Subpulmonary malalignment	VSD closed; arterial switch (aged 3 mnths)
3	TH	Prominent VIF	—	—	Senning operation (aged 6 mnths)
4	Kinking	Prominent IS and VIF	—	—	Mustard operation (aged 1 yr)

COA, coarctation of the aorta; IS, infundibular septum; TH, tubular isthmus hypoplasia; VIF, ventriculoinfundibular fold; VSD, ventricular septal defect.

ventricle; angiograms of patients with transposition but without aortic arch anomalies and 15 normal heart specimens from subjects of different ages served as controls. The ventricular septal defects were classified according to Soto *et al*[5]; in addition we used the term "subpulmonary malalignment" for defects with rightwards shifting of the infundibular septum and overriding of the pulmonary artery. The right ventricular muscular structures were described according to the terminology proposed by Anderson *et al.*[6]

Tubular hypoplasia of the aortic isthmus was defined as a combination of abnormally great length and small diameter of that segment according to the criteria given by Moulaert *et al.*[7]

Using Hegar dilators, the tricuspid valve annulus was measured in relation to the mitral valve annulus. The tricuspid valve was considered to be hypoplastic if its diameter was <0·8 of that of the mitral valve.[8]

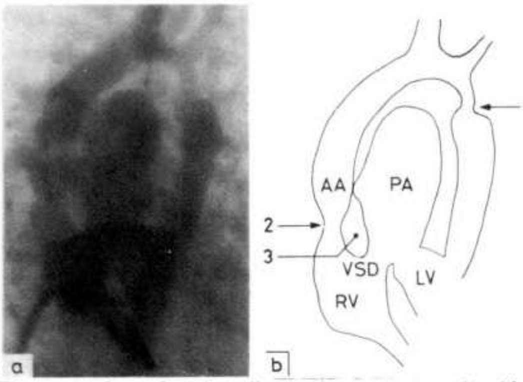

Fig. 1 *(a) Lateral angiocardiogram in neonate (case 2) with transposition of great arteries, subpulmonary malalignment ventricular septal defect, isthmus hypoplasia, and mild subaortic narrowing. (b) Schematic drawing of the angiocardiogram. AA, ascending aorta; LV, left ventricle; RV, right ventricle; PA, pulmonary artery; VSD, ventricular septal defect; 1, isthmus hypoplasia; 2, mild subaortic narrowing; 3, infundibular septum.*

Results

SURVIVORS

Four patients were alive and well six months to five years after operation (Table 1). In two of these patients (cases 1 and 2) a subpulmonary malalignment ventricular septum defect was closed, and the other two had an intact ventricular septum. The subpulmonary malalignment defects were angiocardiographically characterised by overriding of the pulmonary artery; in addition, right ventriculography showed muscular subaortic stenosis caused by an anteriorly displaced infundibular septum and prominence of the ventriculoinfundibular fold (Figs. 1 and 2).

The angiocardiogram of the patient with kinking of the aorta and an intact ventricular septum (case 4)

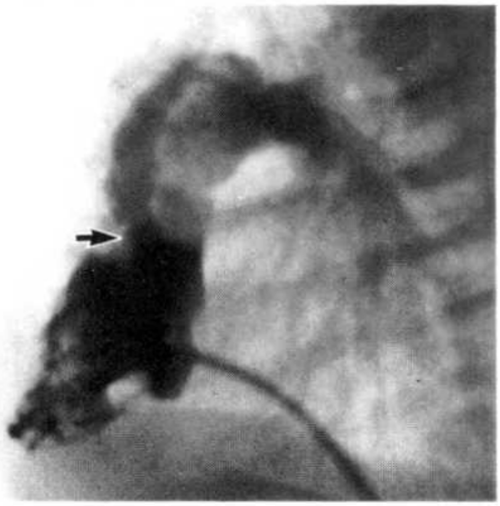

Fig. 2 *Lateral right ventriculogram in neonate (case 1) with transposition of great arteries, subpulmonary ventricular septal defect, and local coarctation (not visible in this frame). Note subaortic stenosis (arrow) and relatively anterior position of wide pulmonary artery.*

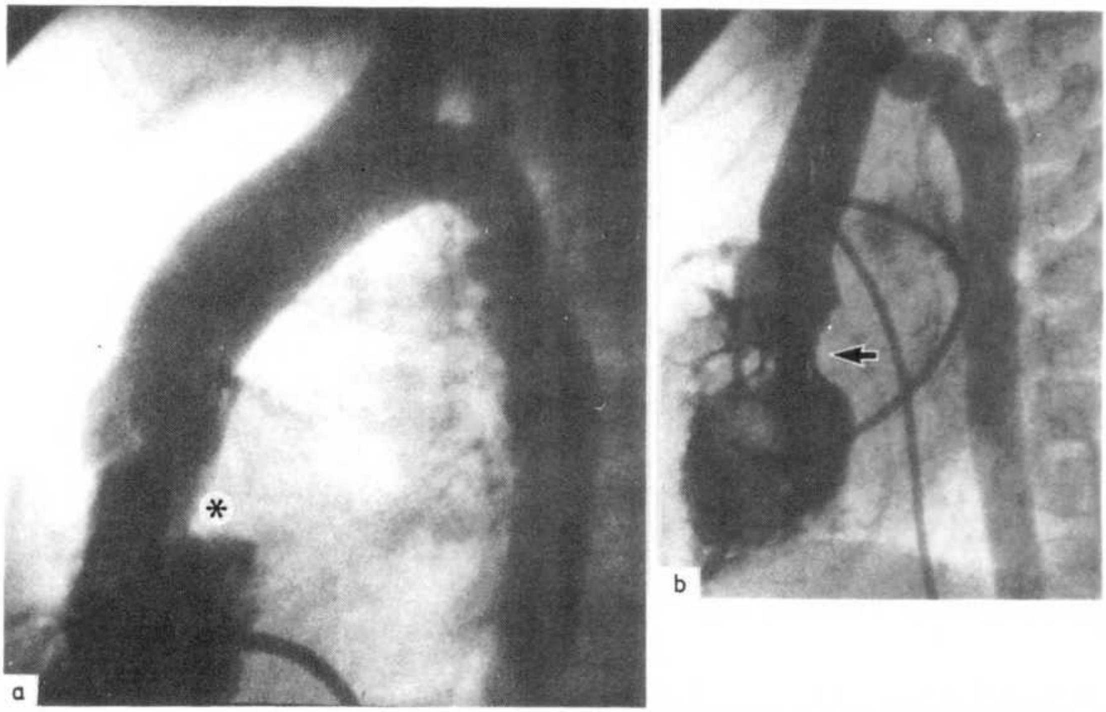

Fig 3 *(a) Lateral right ventriculogram in a 1 year old child (case 4) with transposition of the great arteries and kinking of the aorta. Note the prominence of the infundibular septum (asterisk); frame taken during ventricular diastole. (b) Left oblique view in the same patient; frame taken during ventricular systole. Note the subaortic stenosis (arrow) caused by infundibular septum and ventriculoinfundibular fold.*

showed prominence of the infundibular septum in the lateral view (Fig. 3a) and of the ventriculoinfundibular fold in the left oblique view (Fig. 3b). Another example of prominence of the ventriculoinfundibular fold is shown in Fig. 4. Regarding the aortic arch of the survivors, one local coarctation has been resected, one hypoplastic isthmus has grown to normal dimensions, and two of the patients await an eventual operation.

NON-SURVIVORS

Ten patients died before or after operation (Table 2). Six of the necropsy specimens showed a subpulmonary ventricular septal defect (cases 5–10). This type of defect is, as has been described before,[9] characterised by anterior displacement of the infundibular septum and prominence of the ventriculoinfundibular fold; this results in a reduction in distance between these structures and the anterior right ventricular wall and thus in narrowing of the outflow tract (Fig. 5). This close relation between (type of) ventricular septal defect and outflow tract narrowing was absent in the other four specimens, of which one showed a perimembranous trabecular defect, one a very small muscular inlet defect, and two an intact septum. In these four cases either redundant muscle tissue obstructed the outflow tract (three hearts) or the inflow tract was obstructed by a hypoplastic tricuspid valve or both. Two cases (cases 13 and 10) of hypoplastic tricuspid valves and redundant outflow tract muscle tissue (a prominent ventriculoinfundibular fold and a trabecula in front of the aortic ostium) are shown in Figs. 6 and 7.

Valid catheterisation data were available for eight patients. In only one of these patients a pressure gradient (of 30 mmHg) was present across the right ventricular outflow tract.

Discussion

The findings in this study show that in all cases of transposition of the great arteries and narrowing of the aorta, anatomical right ventricular outflow or inflow tract obstruction or both are present. Milanesi *et al* came to the same conclusion,[4] and we agree with these authors that unequal partitioning of the blood flow as a consequence of right ventricular obstruction may be the fetal pathogenetic mechanism for the

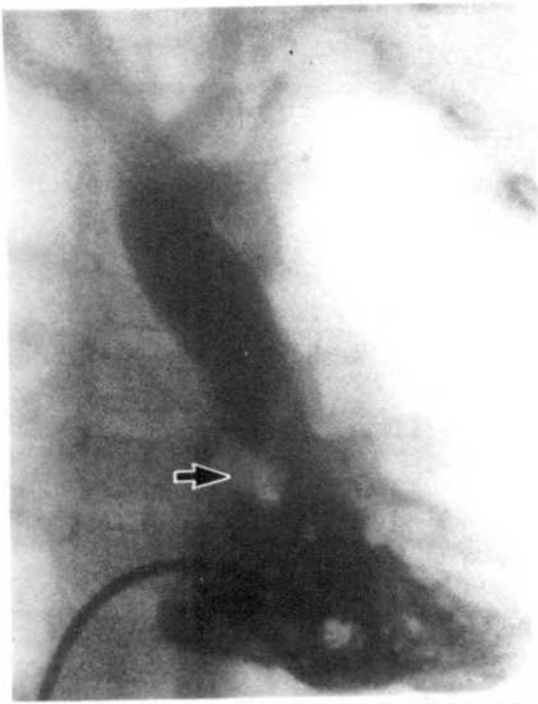

Fig. 4 *Right ventriculogram in 8 month old child (case 12) with transposition of the great arteries and local coarctation, which is hidden behind the ascending aorta in this frontal view. Note the subaortic narrowing by undue prominence of the ventriculoinfundibular fold (arrow).*

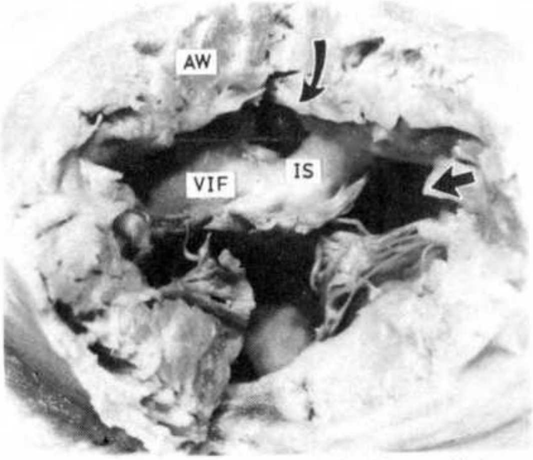

Fig. 5 *Morphological appearance of the right ventricle in a patient (case 5) with subpulmonary ventricular septal defect (arrow). Anterior displacement of the infundibular septum (IS) and prominence of the ventriculoinfundibular fold (VIF) narrow the outflow tract (curved arrow). AW, anterior wall of the right ventricle.*

underdevelopment of the aortic arch, as postulated for left ventricular outflow tract obstruction in normally related great arteries.[10 11] Eight out of 14 patients proved to have a subpulmonary malalignment ventricular septal defect with anterior and rightward displacement of the infundibular septum. A rightward shift of the infundibular septum is also an essential feature of double outlet right ventricle with subpulmonary ventricular septal defect; the difference between transposition and double outlet right ventricle is evident by the degree of rightward shifting of the infundibular septum and thus by the degree of pulmonary artery overriding. Since the frequent concurrence of double outlet right ventricle and aortic arch anomalies has been established before (Kurosawa H, van Mierop LHS. World Congress of Paediatric Cardiology, London, 1980, abstract No 339),[12-14] we selected for the present study cases of transposition according to the 50% rule—that is, in our cases the pulmonary artery was mainly committed to the left ventricle.

Table 2 *Anatomical features of cases examined at necropsy*

Case No	*Age*	*Aortic arch anomaly*	*Right ventricle*		*VSD*
			Outflow tract	*Inflow tract*	
5	5 mnth	TH	Anterior displacement of IS and VIF	—	Subpulmonary malalignment
6	4 mnth	TH	Anterior displacement of IS and VIF	—	Subpulmonary malalignment
7	2 wk	TH	Anterior displacement of IS and VIF	—	Subpulmonary malalignment
8	1½ yr	COA	Anterior displacement of IS and VIF	—	Subpulmonary malalignment
9	1 mnth	COA	Anterior displacement of IS and VIF	—	Subpulmonary malalignment
10	1 mnth	COA	Anterior displacement of IS and VIF	Hypoplastic TV	Subpulmonary malalignment
11	1 mnth	COA	—	Hypoplastic TV	—
12	8 mnth	COA	Prominent VIF	—	—
13	2 mnth	TH	Trabecula ventral to aortic ostium	Hypoplastic TV and right ventricle	Small muscular inlet
14	3 mnth	Isthmus atresia	Prominent IS and VIF	Hypoplastic TV	Perimembranous trabecula

COA, coarctation of the aorta; TH, tabular isthmus hypoplasia; IS, infundibular septum; VIF, ventriculoinfundibular fold; VSD, ventricular septal defect; TV, tricuspid valve.

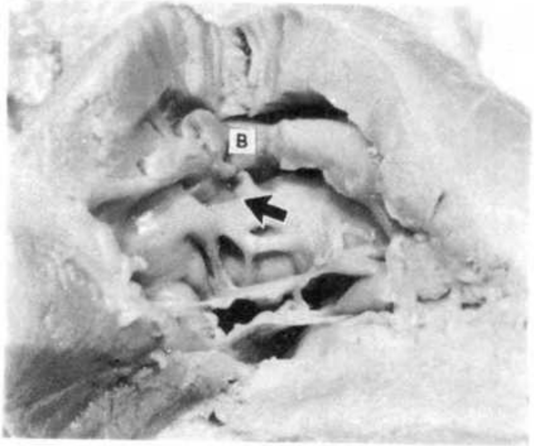

Fig. 6 *Morphological specimen in case 13 showing narrowing of the right ventricular outflow tract (arrow) by an aberrant hypertrophic muscle bundle (B) in front of the aortic ostium. Note the hypoplasia of the tricuspid valve.*

In a previous anatomical study we found aortic arch anomalies in 35% of hearts with transposition of the great arteries and right ventricular outflow tract obstruction.[9] It should be noted that the diagnosis of right ventricular outflow tract obstruction is an estimation, and in that as well as in the present study it means an obstruction relative to normal. In this respect it is important to realise that in only a few patients with an obvious, angiocardiographically demonstrated, narrow subaortic area may a pressure gradient be recorded across it.[4 9 15] Nevertheless, a poorly expanded or relatively narrow subaortic conus should be viewed as potentially obstructive according to Freedom *et al.*[15] In our view more studies of the relation between anatomical right ventricular obstructions and catheterisation data are needed to establish the functional implications and natural history of these anomalies.

Milanesi *et al* suggest that the combination of transposition of the great arteries and coarctation of the aorta is not so rare and that the clinical manifestations and the pathological findings of this association are sufficiently distinctive as to be considered a separate nosographic entity among transposition of the great arteries.[4] According to these authors, the entity should include the following morphological features: (*a*) a ventricular septal defect, mostly subpulmonary; (*b*) underdevelopment of the right ventricular trabecular component; and (*c*) right ventricular outflow or inflow obstruction.

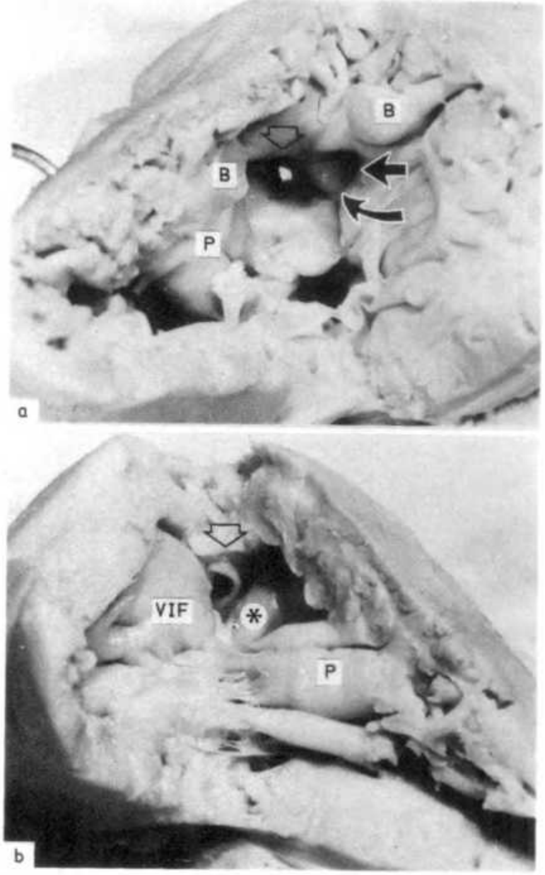

Fig. 7 *Morphological appearance of the right ventricle in a patient (case 10) with subpulmonary ventricular septal defect (arrow). (a) A displaced infundibular septum (curved arrow) narrows the outflow tract (open arrow). A cut aberrant muscle bundle (B) crosses the right ventricular cavity. The hypoplastic tricuspid valve is connected with an abnormal, thick parietal papillary muscle group (P). In this view the ventricle is opened with an incision along the ventricular septum. (b) The same right ventricle opened by a more parietal incision showing the outflow tract (open arrow), which is narrowed by a displaced infundibular septum (asterisk) and a very prominent ventriculoinfundibular fold (VIF). Note the abnormal thick papillary muscles (P).*

Our study confirms the presence of angiocardiographic or anatomical outflow or inflow obstruction or both in all cases. Nevertheless, underdevelopment of the right ventricle was diagnosed only once as a separate feature; in all other cases the trabecular part was not hypoplastic, although in some cases outflow tract obstructing muscle bundles protruded into the trabecular part as well, thus reducing the trabecular lumen.

Another difference between our findings and those of Milanesi *et al* applies to the obligatory presence of a ventricular septal defect in their cases; in our patients four (28%) proved to have an intact ventricular septum. Since, in addition, the type of aortic arch anomaly may differ (from atresia via tubular hypoplasia and local coarctation to kinking of the aorta) we conclude that the variety of these findings does not justify the definition of a nosographic entity.

This conclusion implies that a general prognosis cannot be given for the group as a whole and that the surgical results depend on the presence or absence of an intact ventricular septum and the type and degree of aortic arch anomaly. In this respect it is important to realise that, although most cases had distinct narrowing of the aorta, in other cases the narrowing may be mild; this was the case in some patients with tubular hypoplasia of the isthmus, in one of which the isthmus grew spontaneously to normal dimensions.

The hospital mortality has been high in the earlier years of our experience; recent results support the feasibility of successful surgical treatment. In this context, however, the maintained systemic right ventricular blood pressure may trigger hypertrophy, eventually resulting in progression of the outflow obstruction; as we indicated before[9] this progression might be prevented by performing an arterial switch procedure with resulting normalisation of right ventricular pressure.

Indications for surgical treatment of right ventricular outflow and inflow tract obstruction should be based on the results of functional and natural history studies, which have not been performed as yet.

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Treatment of tachycardias associated with the Wolff-Parkinson-White syndrome by transvenous electrical ablation of accessory pathways

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SUMMARY Three patients with tachycardias associated with the Wolff-Parkinson-White syndrome had failed to respond to antiarrhythmic drugs and underwent transvenous ablation of accessory pathways. Intracardiac studies located the site of accessory pathway to the septum in two patients and mid-posterobasal left atrioventricular junction in one. Ablation was performed by positioning an electrode lead as close as possible to the accessory tract and delivering shocks of 50 to 100J using a conventional defibrillator. In all patients the accessory pathway was abolished after the first three shocks. In two patients followed for four and nine months there was no recurrence of tachycardia or pre-excitation. The other patient developed pre-excitation again three weeks later and repeat ablation was performed. This patient has been followed for six months with no evidence of a recurrence of pre-excitation.

This method may provide a valuable alternative to pacemaker and surgical treatment in selected patients with drug resistant arrhythmias associated with accessory atrioventricular connexions.

Transvenous pacing and ablation techniques[1 2] are emerging as important alternatives to drug and surgical treatment for the control of recurrent tachycardias. Pacemakers are usually considered in patients who have failed to respond to drugs or cannot tolerate them for various reasons. There are, however, some situations where pacemaker treatment is not appropriate or the patient is unwilling to consider implantation of a device. Until recently, ablation could be performed only by surgical intervention.[3] Transvenous ablation of atrioventricular nodal pathways has been successfully used to control a variety of atrial and junctional arrhythmias by several investigators[4–6] and it is likely that this technique will supplant surgical ablation of atrioventricular pathways. Fisher and colleagues have modified this technique to ablate accessory pathways in patients with the tachycardias associated with the Wolff-Parkinson-White syndrome.[7] In this report we describe a similar method which was successfully used in three patients with this syndrome.

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Patients and methods

The three patients were referred for investigation and treatment of tachycardias associated with the Wolff-Parkinson-White syndrome. The Table summarises the clinical details. Transvenous ablation was considered because drugs had either failed or produced intolerable side effects.

ELECTROPHYSIOLOGICAL STUDIES

Standard electrophysiological techniques were used as described previously.[8] Bipolar or multipolar electrodes with 1 cm interelectrode distances were used for stimulation and recording. The clinical arrhythmia was initiated in each patient. In two patients (cases 2 and 3) mapping of the atrial activation sequence was performed during atrioventricular re-entrant tachycardia. In both cases, earliest atrial activation was found in the coronary sinus region indicating a left direct atrioventricular connexion.[9] In the patient in case 2 the pathway was localised to the mid-coronary sinus and that in case 3 to the septal region. In the patient in case 1, the accessory pathway conducted only anterogradely and localisation was

Table *Clinical details and results*

Case No	*Age (yr)/ sex*	*ECG pattern*	*Symptoms*	*Drugs*	*Side effects*	*Details of shocks*	*Peak CPK activity*	*Follow up*
1	33 M	WPW type A	Palpitation Syncope	Disopyramide	Ineffective	50, 80, 80, 100 J	260 IU/l	3 Weeks
				Flecainide	Rash	50, 80×5 J (at second attempt)	304 IU/l (MB 29, 16)	6 Months
				Amiodarone	Did not want drug			
2	26 M	WPW type A	Palpitation	Disopyramide	Ineffective	50, 80, 80, 100×3 J	1024 IU/l	9 Months
				Digoxin	Ineffective			
				Propranolol	Ineffective			
				Verapamil	Ineffective			
				Flecainide	Ineffective			
				Amiodarone	Thyrotoxicosis			
3	31 F	WPW type A	Palpitation	Amiodarone	Photosensitivity	80, 80, 50×8 J	Not done	4 Months
				Flecainide	Ineffective			
				Sotalol	Ineffective			

WPW, Wolff-Parkinson-White; CPK, creatine phosphokinase.

achieved by finding the shortest interval between atrial stimulation and ventricular activation while pacing at various sites in the coronary sinus.[10] In this patient, the pathway was located to the septal region.

CORONARY ARTERIOGRAPHY

After detailed electrophysiological studies, selective left coronary arteriography using the Judkins' method[11] was performed to define the anatomy of the left circumflex coronary artery and its branches and the coronary sinus and the relation of these structures particularly in the region of the accessory pathway. In all patients the left coronary artery was non-dominant and the marginal branches were remote from the coronary sinus at the location of the accessory pathway. The coronary sinus itself was of reasonable size (about 1 cm in diameter) as estimated by using the interelectrode distance as a guide.

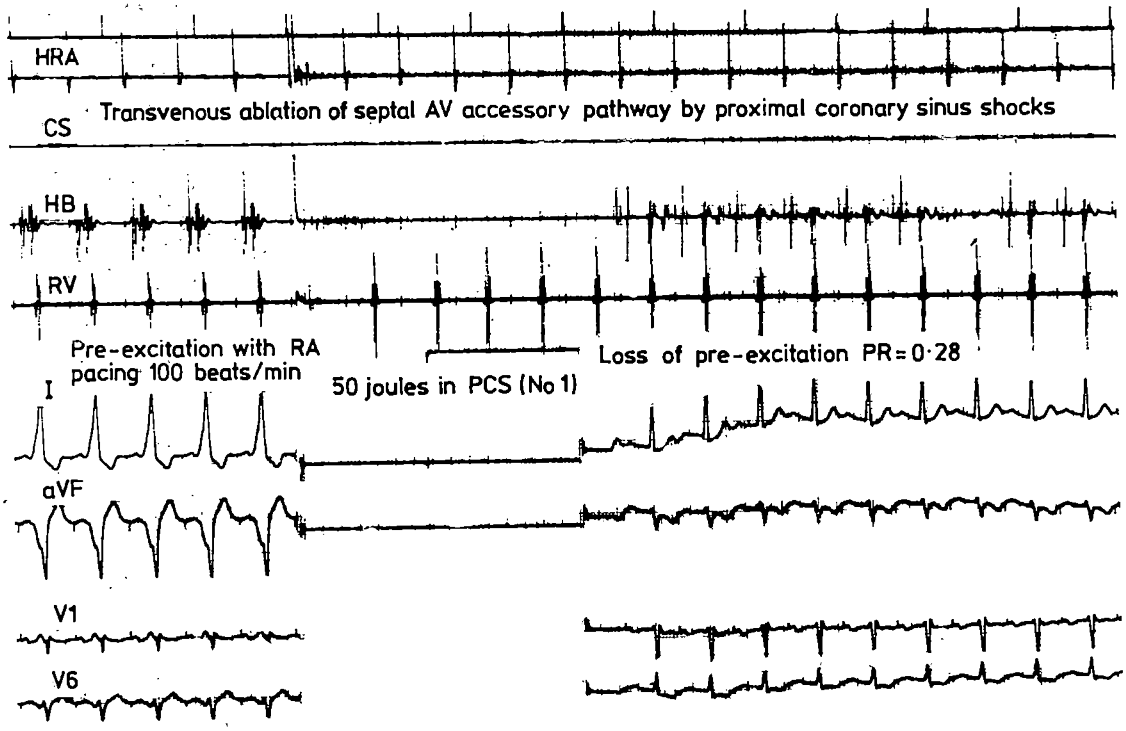
HRA
Transvenous ablation of septal AV accessory pathway by proximal coronary sinus shocks
CS
HB
RV
Pre-excitation with RA pacing 100 beats/min
50 joules in PCS (No 1)
Loss of pre-excitation PR=0·28
I
aVF
V1
V6

Fig. 1 *Electrogram and electrocardiogram showing effect of 50 W s shock to the distal pole (case 1). During atrial pacing ventricular pre-excitation is evident. Immediately after the shock normal QRS complexes appear. The PR interval is prolonged but returned to normal within several minutes. There is obvious ST segment depression and T wave inversion in lead aVF. This recording was taken at the first attempt at ablation. AV, atrioventricular; RA, right atrium; PCS, proximal coronary sinus; HRA, high right atrium; CS, coronary sinus; HB, His bundle region; RV, right ventricular apex; I, aVF, V1, V6, surface ECG leads.*

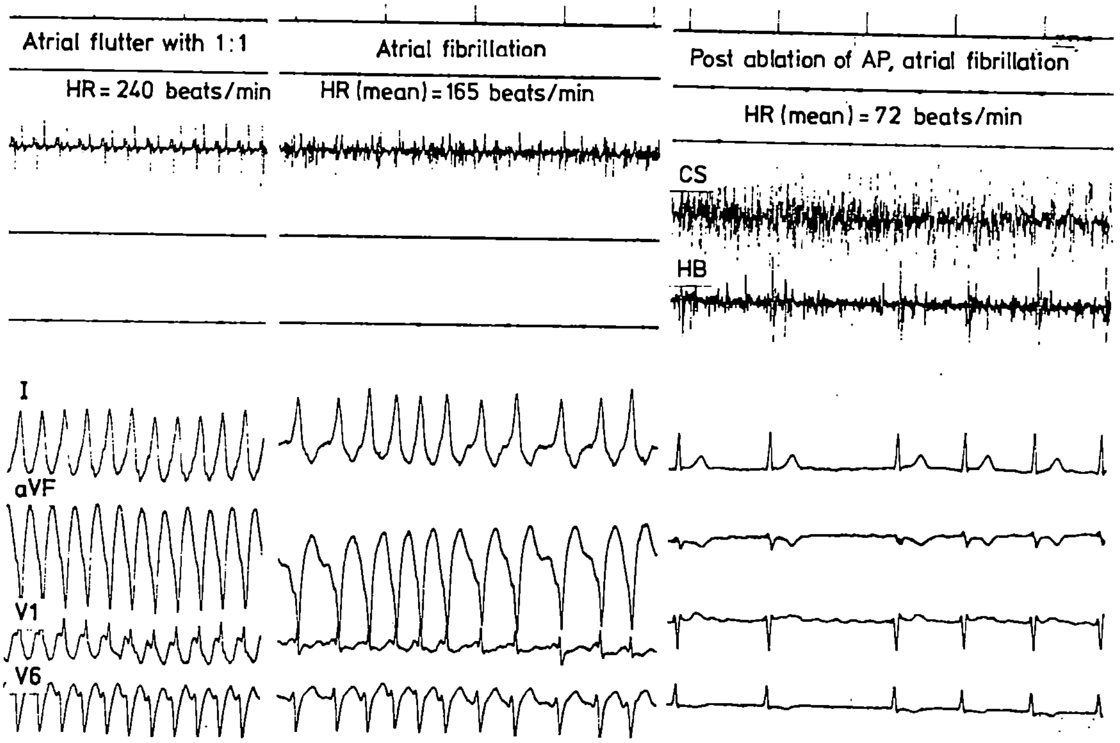

Fig. 2 *Electrogram and electrocardiograms recorded during atrial flutter or fibrillation before and after ablation of accessory pathways (case 1). Before ablation, atrial flutter results in 1:1 atrioventricular conduction and a rapid rate. Atrial fibrillation results in a mean rate of 165 beats/min with a minimum RR interval of 210 ms (not shown). After ablation, atrial fibrillation conducts over the normal pathway with a controlled ventricular response. AP, accessory pathway; CS, coronary sinus; HB, His bundle region; HR, heart rate; I, aVF, V1, V6, surface ECG leads.*

ABLATION TECHNIQUE

Ablation of accessory pathways was performed using an adaptation of the technique previously described for ablation of the atrioventricular node-His bundle.[6] A new 6F or 7F (USCI) bipolar or quadripolar electrode was positioned in the coronary sinus as close as possible to the accessory pathway. Either the distal or the next most proximal pole was attached to a standard defibrillator using an adaptor, and between 4 and 10 synchronised shocks of 50 to 100 J were delivered with the anode positioned at various sites on the anterior chest wall. The positioning of the anode was arbitrary but attempts were made to cover a wide area on the assumption that a vectorial element of the discharge (electrical or mechanical) might be essential to the success of the method. The position of the electrode lead was kept more or less constant for all the shocks; some movement during the shock was, of necessity, unavoidable.

Results

In two patients (cases 1 and 2) pre-excitation disappeared after the first shock (Fig. 1) and in the third patient after the third shock. After the procedure, atrial pacing failed to show ventricular pre-excitation even when combined with isoprenaline infusion. Atrial fibrillation was reinitiated in the patient in case 1, and there was no evidence of pre-excitation (Fig. 2). In no patient could re-entrant tachycardia be started and retrograde conduction was absent. In two patients serum was taken for creatine phosphokinase estimations within one hour and again 10 hours later; the MB fraction was measured in one patient. Repeat studies before discharge failed to elicit tachycardia in the two patients with atroventricular re-entry, and in no patient was there any evidence of pre-excitation.

The patients were followed from four to nine months (Table). Both patients who presented with re-entrant tachycardia were free of attacks without treatment. The patient with atrial fibrillation (case 1) had a recurrence of attacks at three weeks, and on the electrocardiogram pre-excitation was found to have recurred. At restudy, ventricular pre-excitation was confirmed, and the minimum RR interval as a result of accessory conduction was 290 ms during atrial pacing compared with 190 ms during atrial fibrillation or atrial pacing before ablation. Atrial fibrillation was not induced at the second study. In view of the continued potential for rapid ventricular rates, a second attempt at ablation was undertaken using six shocks (Table). This was successful and symptoms have not returned over six months' follow up.

In all patients subsequent electrocardiograms and 24 hour tape recordings showed normal QRS complexes. Inferior T wave inversion noted immediately after ablation in one patient (case 1) (Fig. 1) gradually disappeared. No adverse effects were detected. None of the patients required antiarrhythmic drug treatment.

Discussion

Transvenous ablation of atrioventricular pathways has now been successfully applied by several groups.[4-6] Most of these patients have had refractory atrial or junctional tachycardias, and the aim has been to induce complete atrioventricular block to prevent a rapid ventricular response. In not all cases was this achieved permanently, but the anatomical substrate for tachycardia was damaged and tachycardia did not recur despite resumption of sinus rhythm. In one such patient the tachycardia was intranodal re-entrant in type.[6] After ablation there was first degree atrioventricular block, but no tachycardias could be induced. In other patients, an accessory pathway was inadvertently ablated during attempted ablation of atrioventricular conduction,[4 12] and the patients remained free of tachycardias despite continued atrioventricular conduction. Thus selective ablation of the tachycardia mechanism avoiding induction of atrioventricular block is possible. This is preferable because it obviates the need for permanent pacing. In patients with refractory atrioventricular tachycardias associated with the Wolff-Parkinson-White syndrome ablation of the accessory pathway rather than the atrioventricular non-His bundle is the procedure of choice.[13] The ability to abolish accessory conduction by a transvenous method would, therefore, represent a considerable advance. This possibility was explored by Brodman and Fisher.[14] They delivered low energy shocks of between 35 and 45 J in the coronary sinus of dogs and subsequently found localised histological changes in the atrial wall and atrioventricular groove. They speculated that such damage might be sufficient to ablate conduction in direct left atrioventricular accessory connexions. They also presented preliminary data on the use of this technique in four patients.[7] Energy levels of 60–80 J were delivered via an electrode in the coronary sinus. Complete block of accessory conduction was not achieved in any patient but a symptomatic improvement was noted in all. In some patients they found that the accessory pathway became more sensitive to antiarrhythmic drugs.

The present report further confirms the feasibility of this technique for ablation of left sided accessory pathways near the ostium of the coronary sinus. We have been reluctant, however, to apply shocks to the distal coronary sinus region especially when the diameter of the sinus is not much greater than that of the electrode. We also have reservations about delivering shocks in the coronary sinus if the circumflex artery is in close approximation to the sinus. Brodman and Fisher noted intimal hyperplasia in dogs, but there was no angiographic abnormality of the coronary artery.[14]

The energies we used are similar to those applied by Fisher *et al.*[7] Our higher success rate may have been the result of a more favourable relation between electrode and accessory pathway. Nevertheless, unlike these authors, we chose to use an external anode plate rather than two poles of the electrode. Whether the movement of the anode over the anterior chest wall increases the likelihood of permanently impairing accessory conduction is not known. These differences in technique may account in part for the discrepancy between our results and those of Fisher *et al.*[7] The evidence of Brodman and Fisher suggests that multiple lower energy shocks are safer and more effective than a single high energy shock.[14] There is as yet no information about the optimum number of shocks that may be given. We have not used energies greater than 100 J because they may rupture the coronary sinus.[14] In a recently published case report accessory conduction was abolished by two shocks of 400 J delivered to the ostium of the coronary sinus.[15] This patient was followed for nine months without recurrence of pre-excitation or tachycardias. As yet, we have no experience of transvenous ablation of right sided pathways. In one such patient, Weber and Schmitz used two shocks of 150 J in the right atrium which caused transient abolition of pre-excitation.[16] Failure to achieve block may have been related to difficulties in accurately localising right atrioventricular accessory pathways.[9] The ability to record potentials from accessory pathways[17] may enhance the success of this technique. Jackman *et al* did not, however, achieve permanent ablation of accessory pathways despite having recorded potentials from the region of the accessory pathway.[18] The feasibility and utility of this recording method remains to be evaluated.

No side effects were noted. In particular there was no evidence of significant myocardial, arterial, or valvar damage. The electrocardiographic changes observed in the patient in case 1 were present immediately after ablation and are likely to have been caused by longstanding pre-excitation. This phenomenon has been well described by Nicolai *et al.*[19] The small rise in creatine phosphokinase MB activity indicates some myocardial cellular damage, but this was not associated with electrocardiographic changes or clinical effects. The reasons for failure of the initial attempt at ablation in one patient are not apparent. It is possible that shocks may cause a temporary stunning of conduction such as has been noted in patients undergoing His bundle ablation.[6] The second attempt may have succeeded where the first failed because of cumulative effects. The decrease in the maximum conduction frequency after the first attempt supports this possibility.

In conclusion, transvenous ablation of accessory pathways is a feasible method of treatment of the Wolff-Parkinson-White syndrome in selected patients. At present, we feel it should be limited to patients with refractory arrhythmias associated with accessory pathways on the right or near to the ostium of the coronary sinus. We would like to emphasise that this method is under evaluation and further information is needed before it can be recommended for more widespread use.

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Br Heart J 1985; 53: 69–71

Case report

Aneurysmal dilatation of left atrial appendage diagnosed by cross sectional echocardiography and surgically removed

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SUMMARY An isolated aneurysmal dilatation of the left atrial appendage was found in an 18 year old girl who presented with atrial fibrillation and an unusual cardiac shadow on routine chest radiographs. The diagnosis was made by cross sectional echocardiography. The giant appendage was excised to remove the risk of systemic embolism and the need for life long anticoagulation.

Case history

An 18 year old girl sought medical advice for headaches and was found to have an irregular pulse. Physical examination was otherwise normal. A chest radiograph showed a normal sized heart with a prominent left heart border (Fig. 1a), which on fluroscopy did not pulsate. The electrocardiogram confirmed atrial fibrillation. Treatment with anticoagulants was started. At 14 years old she developed the Guillain-Barré syndrome, and when in hospital a routine electrocardiogram showed sinus rhythm but no chest radiograph was taken.

Cross sectional echocardiography in the parasternal long axis view showed a normal sized left atrium and mitral valve. There was a narrow, long echo free space behind and lateral to the left ventricle. The space appeared to be continuous with the left atrium. In the apical four chamber view it was obvious that this "pouch" connected to the left atrium, extending along the free wall of the left ventricle (Fig. 1b). Computed axial tomography of the heart confirmed these findings and showed that the pericardium was intact over the aneurysmal atrial appendage. Cardiac catheterisation showed normal intracardiac pressures and no evidence of mitral valve disease. Pulmonary angiography indicated opacification of the shadow in the venous phase and contrast swirled in the "aneurysm" for 20 seconds. There was no visible filling defect in the appendage to suggest a mural thrombus (Figs. 2a and 2b). Amputation of the appendage was recommended to obviate the need for long term anticoagulants to prevent systemic emboli.

Through a left thoracotomy an enormous left atrial appendage was seen to compress and indent the left ventricle. The mitral valve was normal to palpation. The appendage was amputated at its base. Histological examination of the base of the left atrial appendage showed hypertrophied myocardium with an increase in interstitial fibrous tissue and thickening of the endocardium. Two weeks after operation the rhythm reverted spontaneously to sinus rhythm which has remained for 6 months without medication.

Discussion

Aneurysmal dilatation of the left atrium involving the appendage is usually associated with mitral valve disease. Herniation of the left atrial appendage through a pericardial defect may cause it to distend.[1] In the absence of a known predisposing cause the condition has been assumed to be of congenital origin. Only one third of the patients, however, have presented symptomatically before the age of 10 years. Usually the problem is discovered in the second to fourth decades of life.[2] Its discovery in a 10 month old baby[3] suggests that it is of congenital origin or is acquired from a congenital lesion of the left atrial wall.

Histology of the appendage in other patients has shown a similar appearance to that in this case. Whether this results from damage to the atrial wall in intrauterine or postnatal life is not known.

The diagnosis is suggested by the appearance of the cardiac shadow on the chest radiograph. Other conditions which produce a similar shadow are mediastinal

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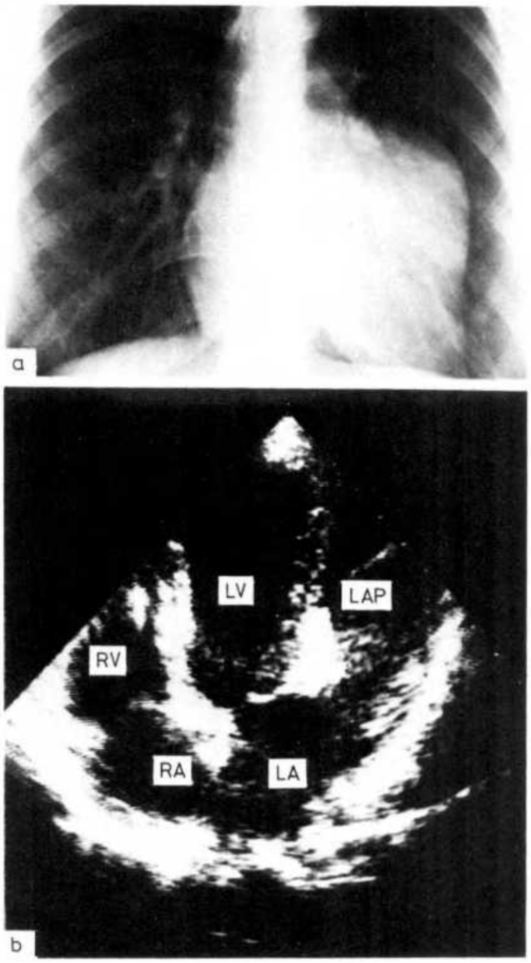

Fig. 1 *(a) Chest radiograph in posteroanterior projection showing a large, rounded mass at the left heart border corresponding to the aneurysm of the left atrial appendage. (b) Cross sectional echocardiogram in the apical four chamber view showing an aneurysmal left atrial appendage (LAP). LV, left ventricle; RA, right atrium; RV, right ventricle.*

and cardiac tumours or pericardial cysts. Angiography has been used to distinguish the condition.[4] In our patient, cross sectional echocardiography but not M mode echocardiography clearly demonstrated the cause of the protuberance of the left heart border showing that the echo free space communicated with the left atrium, which differentiated it from a tumour and a pericardial cyst. Computed axial tomography of the heart was valuable in that it established the relation between the left atrial appendage and pericardium. Cardiac catheterisation was performed to exclude coexisting heart disease but was not necessary to establish the diagnosis.

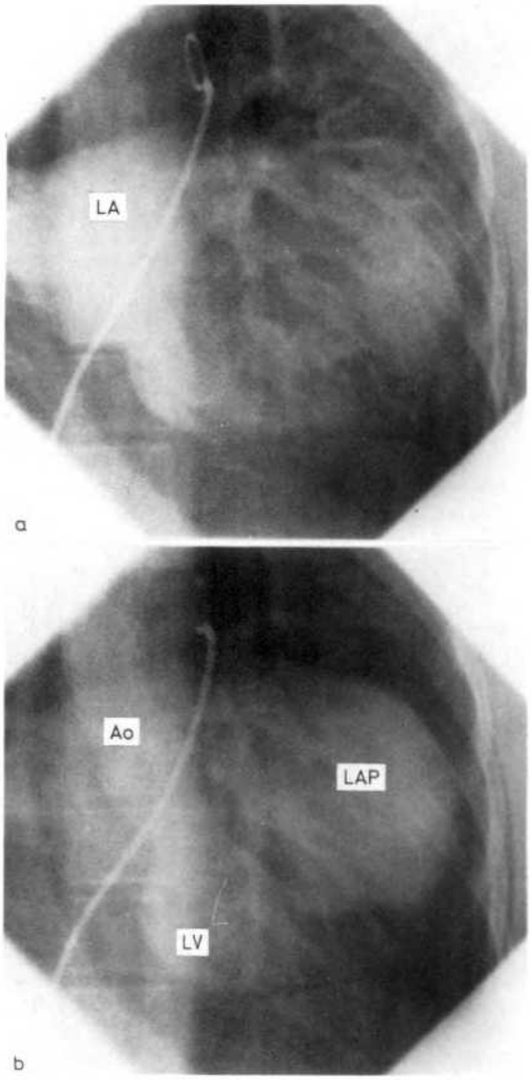

Fig. 2 *Laevophase of pulmonary arteriogram: (a) contrast seen filling pulmonary veins and body of left atrium (LA) with appendage not opacified and (b) later frame with contrast filling left ventricle (LV) and aorta (Ao) but contrast still present in left atrial appendage (LAP).*

Recognition of an isolated aneurysm of the left atrial appendage is important since supraventricular arrhythmias and systemic embolisation are common. The aetiology of the supraventricular arrhythmias is not understood. Perhaps they result from the large area of abnormal atrial wall which allows the development of electrical circus pathways. It is interesting that in other patients the arrhythmia was abolished by aneurysmectomy[5] as in this patient.

Furthermore, aneurysmectomy has, in all the cases reported, resulted in the abolition of systemic emboli.[6]

We thank Mr Donald Ross, for performing the left thoracotomy, and Dr Eckhardt Olsen, for carrying out the histological examination.

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Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre, London, on Monday and Tuesday, 3 and 4 December 1984. The President, MICHAEL OLIVER, took the Chair during private business. At the scientific sessions the Chair was taken by HUGH BENTALL.

Abstracts of papers

Homograft aortic root replacement for complicated prosthetic valve endocarditis

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Thirteen adult patients (mean age 41 years) with prosthetic valve endocarditis or uncontrolled sepsis and aortic root abscesses underwent homograft aortic root replacement with reimplantation of the coronary arteries. There were two perioperative deaths. The endocarditis was cured in all 11 survivors, who have been followed up from 1 to 132 months (mean 33 months). Two of these patients are having symptoms due to homograft valve malfunction; excellent clinical and haemodynamic results have been obtained in the other nine patients.

Homograft aortic root replacement excludes the root abscesses and the weakened infected aortic annulus from the high systemic pressure and permits suturing of the homograft to healthy myocardium. It provides an alternative technique in the management of selected patients with active prosthetic infection and aortic ring destruction by sepsis.

Adult heart valve dimensions and their surgical implications

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After valve replacement, some patients fail to improve in functional status because their prosthesis is restrictive. We believe that for adults, body habitus relates poorly to valve size and that Lev's data relating body surface area to valve size in childhood cannot be extrapolated into adult life. We therefore sought guidelines for valve replacement by measuring valve circumference, then calculated circularised orifice areas in 160 postmortem hearts from adults with and without congestive cardiac failure. Multivariate analysis was used to relate orifice area to age, sex, height, body surface area, and congestive cardiac failure. We found only sex and congestive cardiac failure to have statistically significant relations to valve area, correlation coefficients showing body surface area and other variables to be poorly related. We can therefore state a mean circularised orifice area for each adult cardiac valve and aim to insert an appropriate prosthesis. Male patients have larger valves, and atrioventricular valves are enlarged in congestive cardiac failure. Comparison of mean valve area with the effective orifice area of current prostheses shows, however, the majority (particularly mechanical valves) to be restrictive at rest, especially in the mitral and tricuspid positions. Improved prosthetic design, valve repair wherever possible, and annulus enlargement procedures are required to eliminate this problem.

Early and medium term results of cardiac transplantation with minimum or no oral steroids

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Between February 1980 and August 1984, 124 patients underwent cardiac transplantation at Harefield Hospital with an overall one year survival of 72%. Early in the experience oral steroids were identified as a major cause of morbidity and mortality, particularly in very young and elderly patients. Since September 1982 the immunosupressive protocol consisted of cyclosporin, azathioprine, and antithymocyte globulin with no or minimum 5–15 mg oral steroids/day. During this period 85 patients underwent cardiac transplantation (65 orthotopic and 20 heterotopic). Their ages varied from 16 to 59 (mean 44·7) years. The original disease was ischaemic in 47, congestive cardiomyopathy in 29, valvular in six, and others in three. There were 15 deaths (17·6%) all within the first three months, giving an actuarial one year survival of 82%. Four patients (5%) developed relatively serious infections, which were successfully treated

Eight patients (9%) required treatment for systemic hypertension and three (3·5%) developed lymphoproliferative disease which regressed on reducing immunosupression in two and required excision in one. Twenty five patients, investigated by coronary angiography one year postoperatively, showed no localised or diffuse narrowing (chronic rejection). Graft function has been good in all survivors.

It is concluded that cardiac transplantation can be performed with minimum, or no, oral steroids and that this might help to liberalise the age limits for acceptance.

Development of the clinical heart-lung transplant programme

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Since November 1982 progress has been made towards the development of clinical heart lung transplantation at Papworth Hospital. Between November 1982 and August 1984, there have been 59 referrals for heart-lung transplantation, 42 with primary lung disorders and 17 with primary cardiac defects. Many early referrals did not meet our criteria, primarily because of age or medical unsuitability. Fourteen patients have been assessed for transplantation and six await assessment; nine have been accepted as heart-lung recipients. Two patients with primary pulmonary hypertension on prostacycline therapy have been provisionally accepted. Of the nine patients, three have died waiting. Four patients are currently awaiting transplantation, the major limiting factor being the availability of suitable donor organs. Size compatibility, normal lung function, and clear chest *x* ray appearances are essential.

Between April 1984 and September 1984, two patients have been successfully transplanted, one with fibrosing alveolitis and one with Eisenmenger's syndrome secondary to an atrial septal defect. The patients are alive and well at six months and one month following transplantation with excellent cardiopulmonary function, $Po_2 > 11$ kPa on air. We have introduced a new method of preserving donor lungs prior to transplantation, the preservation solution being colloid rather than crystalloid based. This has in our initial experience produced excellent early postoperative pulmonary function. Immunosuppression consisted of cyclosporin A, low dose steroids, and a short course of equine antithymocyte globulin. Imuran has not been used. Combined heart and lung transplantation is a viable clinical procedure for selected young patients with lethal and disabling pulmonary or cardiopulmonary disease.

Preoperative predictability of the late clinical outcome after CABG in patients with severe ventricular dysfunction

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The predictability, based on preoperative factors, of the late clinical outcome after pure coronary artery bypass grafting is evaluated in 60 patients with a severe ventricular dysfunction (mean ejection fraction (EF) 31·8% and mean end diastolic pressure 17·6 mm Hg).

Actuarial total survival, cardiac survival, and event-free curves, angina, and NYHA classification at 12 and 18 months postoperatively, made for 15 preoperative variables, define the late clinical result. The cardiac operative mortality was 0% for the 35–45% EF subgroup, 0% for the 25–34% EF subgroup, and 20% for the under 24% EF subgroup. The 24 months actuarial cardiac survival was 93% for the patients with a 35–45% EF, 93% for the patients with a 25–34% EF, and 43% for those with an EF under 24%.

A mathematical model was constructed and the mortality predictability at 18 months was analysed by stepwise logistic regression. The best prediction was obtained using the ejection fraction and the preoperative NYHA functional class with 91·7% correct predictions, a sensitivity of 72·7%, and a specificity of 95·9%. The rank correlation between the predicted probability and the response was 0·922. Other variables did not increase the accuracy.

$$\text{Probability} = \frac{e^{-1\cdot63\ -0\cdot28 \times \text{EF}\ +2\cdot95 \times \text{NYHA}}}{1 + e^{-1\cdot63\ -0\cdot28 \times \text{EF}\ +2\cdot95 \times \text{NYHA}}}$$

This formula can help to define the patients with poor ejection fraction but very good clinical outcome and those in whom the high operative risk cumulates with poor late survival.

Myocardial revascularisation during acute infarction

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Thirty two patients were operated on during the acute phase of myocardial infarction. Their mean age was 53·7(6·8) years (range 36–69). Of the patients (26 male and six female), 37% had previously suffered from another myocardial infarction. All patients were accepted for surgery whatever their clinical condition; 50% were in carcinogenic shock or receiving cardiac resuscitation. Myocardial revascularisation to the threatened area was finished in 18 patients less than 150 minutes after the onset of ischaemia, with a mean of 183·5(88·5) minutes. A mean of 2·3 distal anastomoses were constructed per patient. The operative mortality was 9·3%. The operative survivors were followed for 15·5(8·3) months; all are alive at the end of follow up and 95·7(4·1)% stayed angina free.

Postoperative radionuclide assessment, more than two months after surgery, showed significantly smaller thallium defects and better ejection fractions than controls (n=20), who received conventional treatment for acute myocardial infarction, when surgery was finished within two hours. When revascularisation was completed more than four hours after the onset of symptoms, the scintigrams were not different from the controls. Electromicroscopical studies of epicardial and endocardial biopsies from the centre of the area at risk correlate with the radionuclide findings.

Coronary surgery can be performed in the acute phase of the myocardial infarction but should be limited to the early revascularisations if the damage to the cardiac function wants to be preserved.

Inhibition of implanted pacemakers by domestic electrical appliances

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Unipolar ventricular inhibited demand cardiac pacing is the usual mode of treatment for symptomatic bradyarrythmias. Demand (VVI) pacemakers are susceptible to electromagnetic interference which may cause return of symptoms depending upon the duration of induced inhibition and the patient's underlying spontaneous rhythm. Various methods have been tried to avoid external electromagnetic interference by metal housing of the unit and by modification of the pulse and amplitude discriminating sensing circuit. Because of the increasing use of electrical domestic appliances, the sources of electromagnetic interference are growing rapidly. It is important to have a working knowledge of the behaviour of modern pacemakers in the presence of such potential hazards.

Fifty four patients with implanted pacemakers of different manufacturers were tested against common domestic mains electrical appliances operating in close proximity to the unit at variable distances: shaver, hairdryer, food processor, domestic drill, hedge clipper, vacuum cleaner, and microwave oven. Significant pacemaker inhibition was induced in 37 patients by equipment operating at less than 22·5 cm proximity. The domestic drill (91%) and the hedge clipper (41%) were the main inhibitors. The shaver also affected a small number (7) of the patients.

This preliminary study demonstrates that some domestic electrical appliances can seriously interfere with pacemaker function. Operation of the equipment tested appears, however, to be safe beyond a distance of 30 cm.

Left ventricular dynamics during exercise in physiological and non-physiological pacing modes using gated radionuclide angiography

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Left ventricular dynamics have been compared during physiological ventricular fixed rate and externally triggered rate responsive ventricular pacing. Measurements of ventricular function were made using equilibrium gated radionuclide angiography at rest and during steady state exercise. Fifteen patients in complete heart block treated with programmable VAT or DDD pacemakers were studied first in the VAT mode and 14 days later in the VOO mode. In five of these patients an additional mode, externally triggered rate responsive ventricular pacing without atrioventricular synchrony, was employed. Indices of left ventricular volumes, cardiac output, and ejection fraction were derived. Comparing VAT and VOO modes two groups of patients could be identified according to the response of stroke volume on exercise in the VAT mode. Those able to increase stroke volume on exercise (8) had a larger rise in cardiac output ($p<0\cdot02$), which was achieved by rate responsiveness and an increase in end diastolic volume. Comparison between the VAT and externally triggered ventricular pacing modes showed similar cardiac outputs at the same ventricular rates on exercise, but with atrioventricular synchrony the end diastolic volume was larger ($p<0\cdot01$).

It is concluded that (*a*) provided stroke volume can increase, cardiac output is improved by physiological pacing and (*b*) atrioventricular synchronous pacing causes a higher end diastolic volume than ventricular pacing at the same rate.

Digital analysis of atrial electrograms: a means of preventing pacemaker mediated re-entry tachycardia?

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The inability of current pacemaker sensing circuits to distinguish anterograde from retrograde atrial depolarisation contributes to the genesis of pacemaker mediated re-entry tachycardia (PMRT). Slew rate analysis of digital atrial signals may overcome this problem.

Using temporary bipolar electrodes, electrograms were recorded simultaneously from three right atrial sites (appendage, high and low lateral) during sinus rhythm and right ventricular pacing in 10 patients with intact retrograde (V-A) conduction. The unprocessed electrograms were analysed for amplitude, slew rate, and signal polarity. These signals were then converted to digital form and further analysed by a slope detection program which displays the original electrogram as a sequence of positive and negative turning points with amplitudes proportional to the original slew rates.

Retrograde atrial signals fulfilled current pacemaker sensing criteria in all patients confirming the potential for PMRT. Significant overall differences between anterograde and retrograde signals were only seen in the slew rates at appendage and low lateral sites: 1·1(0·5) (mean (SD)) *vs* 0·7(0·4) and 1·0(0·4) *vs* 0·7(0·2) V/s respectively ($p<0\cdot05$ for both). Subtle visible differences between the morphology of the analogue anterograde and retrograde electrograms were observed in all patients which would not be detected by simple pacemaker sensing circuitry. Nevertheless, analysis of the digital signal enhanced these differences to the point where anterograde and retrograde depolarisations could be recognised automatically in all patients from 1 or more atrial sites. Digital analysis of atrial signals has successfully distinguished anterograde from retrograde depolarisation and has important future applications in the pacemaker management of iatrogenic and spontaneous tachycardia.

Comparison of burst overdrive, self-searching, and adaptive table scanning programmes in antitachycardia pacing

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Seven patients with the Siemens Elema "Tachylog" generator implanted for the management of their paroxysmal tachycardias were studied to assess the safety and efficacy of three antitachycardia programmes. The modes studied were burst overdrive (BOD), self-search (SS), and adaptive table scanning (ATS). There were four men and three women aged 20–62 years. Six had Wolff-Parkinson-White (WPW) syndrome and one had ventricular tachycardia (VT). Three patients with WPW and one with VT had pacing wires to the right ventricle, the remainder had right atrial pacing electrodes.

All patients were studied acutely lying, standing, and post exercise in all three modes, and the appropriate number and interval of stimuli chosen for the long term programmes. The generator remained in one programme for one month, was interrogated, and the memory read, then reprogrammed to a different antitachycardia mode. BOD was unsuitable for long term use in four patients, producing atrial fibrillation in one and VT in three. In this group SS and ATS were safe and equally effective (mean number of "searches"/attack 6·8 and 6·2 respectively). In the three patients in whom BOD, SS, and ATS could all be safely used BOD proved most efficient, mean number of attempts-tachycardia =3·6 (cf 11·3 for SS and 12·1 for ATS).

Thus careful study and a versatile multiprogrammable generator are neccessary to provide the safest long term antitachycardia programme. Burst overdrive was suitable for only 42% of our patients, but when safe was especially valuable in those with narrow termination windows on exercise.

Continuous measurement of ventricular refractory period and the prediction of imminent loss of capture from the ventricular paced evoked response

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An external pacing system has been designed, which is capable of high fidelity recording of the unipolar evoked electrogram within 5 ms of an applied pacing stimulus. This allows accurate registration of the evoked QRS complex, ST segment, and T wave. There is a marked similarity between the time courses of the paced evoked response and the monophasic action potential recorded from the same site. It should be possible to predict the ventricular refractory period from the evoked stimulus to peak T wave interval (St-T). The ventricular paced evoked response was recorded in five patients during programmed ventricular stimulation. The single ventricular extrastimulus technique was used to determine ventricular refractory period at basic paced cycle lengths of 280–800 ms. The St-T interval measured at each cycle length was then compared with the ventricular refractory period (Vref) at that pacing rate. A linear relation was observed ($Vref=0{\cdot}94\times St\text{-}T-22{\cdot}1$ ms; $r=0{\cdot}98$, $p<0{\cdot}001$) which was highly significant. In addition marked widening and fractionation of the evoked QRS complex was detected when the premature stimulus was delivered within 10–20 ms of the ventricular refractory period.

Similar changes in the evoked QRS complex were also seen with pacing energies less than 2–3 times diastolic threshold in six anaesthetised and thoracotomised dogs. The evoked QRS widened by a mean of 62 ms prior to loss of capture. These preliminary results suggest that prediction of both ventricular refractory period and imminent loss of capture is possible using this device and may find application in future antitachycardia pacemakers.

Blood pressure and symptoms during pacing

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Patients with functioning pacemakers frequently have symptoms of presyncope. We have performed ambulatory monitoring of blood pressure in 10 patients (mean age 67 years) in sinus rhythm originally paced (VVI) for the sick sinus syndrome. They were not taking any cardiovascular medication, and there was no evidence of pacemaker malfunction. Six were asymptomatic and four had symptoms of presyncope. Ambulatory blood pressure recordings were performed using a modification of the "Oxford" system which incorporated a pacing spike detector. From each tape episodes containing at least 20 beats of sinus rhythm followed by 20 beats of paced rhythm were selected. A total of 101 such episodes were analysed. Within each episode zero was defined as the onset of pacing and beats were numbered consecutively in a positive direction (after onset) and negatively (count down to onset). Eleven beat regression analysis of blood pressure on beat number was then performed. The number of quadratic components present at each beat number was then calculated and a χ^2 test performed for systematic deviations between expected and observed distributions. All showed a significant ($p<0{\cdot}01$–$p<0{\cdot}001$) fall in blood pressure with the onset of pacing. In the asymptomatic patients blood pressure recovered within five beats, but in the symptomatic group this recovery was delayed by up to 15 beats. Two symptomatic patients underwent a change of pacemaker to a DVI device. This resulted in the disappearance of symptoms and abolition of the fall in blood pressure. These data suggest that the onset of VVI pacing induces a fall in blood pressure in most patients, but symptoms only appear if baroreflex compensation is impaired. These haemodynamic consequences may be abolished by dual chamber pacing suggesting that baroreflex function should be tested before deciding which pacing mode to use.

Surgical correction of total anomalous pulmonary venous connexion: influence of cross sectional echocardiography and perioperative therapeutic optimisation

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Sixty six patients have been surgically treated for correction of total anomalous pulmonary venous connexion (TAPVC) from 1973 to 1984; 38 were male and 25 female. The median age at operation was 77 days and the median weight 3·8 kg. The anatomic type encountered was infracardiac (IC) in 13, cardiac (C) in 27, supracardiac (SC) in 24, and mixed (MC) in 2. The diagnosis was established by catheterisation and angiography in 47 patients, in three by clinical examination, and in the last consecutive 16 by cross sectional echocardiography alone. Pulmonary hypertension (PHT) was present in 26 (41%) of those patients catheterised preoperatively. Pulmonary vascular resistance (PVR) averaged 8·1 u m^2, and in those with IC >10 u m^2. Conventional (CPB) bypass with profound to moderate hypothermia was used in 14 patients, and preliminary surface cooling then core cooling to 15°C with circulatory arrest in 52. Six patients developed one or more pulmonary hypertensive crises during the postoperative period, in four diagnosed by direct pulmonary artery pressure (PAP) measurement and in two on clinical examination. Late reoperation was necessary in six (11%) patients. Multivariant analysis of risk factors for 30 days survival with regard to sex, year of operation, days in hospital before operation, age, height, weight, body surface area, pH on admission, PAP, PVR, PHT crises, mode of investigation, type of CPB, and type of anatomy showed that risk of early death was increased in respect to PHT crises ($p<0\cdot06$), year of operation ($p<0\cdot02$), and sex of patient ($p<0\cdot02$) but decreased with echo diagnosis alone ($p<0\cdot05$). The 30 day hospital mortality from 1975 to the present time is 11%. The late mortality is represented by six (9·5%) patients. Actuarial survival of IC patients is 69% at 72 months, but the others had 88% survival at 80 months.

Continuous wave Doppler echocardiography in 120 infants and children with congenital heart disease

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Continuous wave Doppler echocardiography has been used to study 120 infants and children (7 days to 15 years) with congenital heart disease undergoing cardiac catheterisation or cardiac surgery without catheterisation. The provisional diagnosis was made with clinical examination and cross sectional echocardiography and the Doppler study directed to sites where a pressure gradient was suspected. The maximum velocity of blood flow was measured and the gradient calculated from the modified Bernoulli formula. An accurate estimate ($r=0\cdot94$) of the gradient was obtained in those with stenotic lesions including pulmonary valve stenosis (26), pulmonary valve and infundibular stenosis (16), aortic stenosis (10), pulmonary stenosis with transposition (4), and pulmonary artery banding (5). A satisfactory estimate of the pulmonary artery pressure in 17 patients with a ventricular septal defect was obtained by subtracting the estimated pressure difference between the ventricles from the systolic blood pressure. In 14 of 15 patients with coarctation of the aorta demonstration of increased velocity in the distal aortic arch confirmed evidence of the site of coarctation; in another failure to demonstrate this suggested complete obstruction. Doppler echocardiography provided information not obtained at catheterisation in six and which was important in undertaking surgery without catheterisation in two.

Continuous wave Doppler echocardiography has been shown to make an accurate assessment of pressure gradients between ventricles, over stenosed ventricular outlets, and across arterial obstructions and is thus an important non-invasive technique in the management of a wide variety of cardiovascular defects.

Clinical value of continuous wave Doppler in adults with aortic stenosis

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Thirty five adults with clinical evidence of aortic stenosis (age range 15 to 71 years) were evaluated using continuous wave Doppler in addition to non-invasive assessment with clinical examination, ECG, chest *x* ray, and cross sectional echocardiography. Doppler examination was performed using a Vingmed Alfred continuous wave Doppler velocimeter in conjunction with spectrum analysis, using a 2 MHz transducer. Doppler gradients were calculated using the modified Bernoulli equation. Peak to peak pressure gradients were obtained independently at cardiac catheterisation in all patients, and simultaneous Doppler examinations performed in 25. There was a good correlation between the two methods ($r=0\cdot92$), in particular when simultaneous Doppler recordings were obtained ($r=0\cdot98$). When the complete non-invasive assessment of these patients was evaluated, all those with a surgically significant stenosis were correctly identified. In particular, overestimation was not found in any patient with a less than significant obstruction.

In conclusion, therefore, continuous wave Doppler provides an accurate assessment of the degree of aortic stenosis, and in conjunction with other non-invasive techniques obviates the need for catheterisation in these patients.

Assessment of stroke volume and cardiac output by Doppler ultrasound alone

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It has been shown that stroke volume may be calculated from the product of aortic cross sectional area and the systolic velocity integral of aortic blood flow. On theoretical grounds, the systolic velocity integral (stroke distance) would therefore be expected to behave as the stroke volume index, and this was tested in healthy subjects and seven groups of patients. The normal range of aortic blood velocity was established in 140 healthy adults using a non-invasive Doppler ultrasound technique. Integration of the area under the velocity time curve for each beat gives stroke distance, and its product with heart rate gives minute distance. We have shown that stroke distance is independent of sex, body surface area, and blood pressure but shows a progressive decline with age. When compared with age corrected normal values, stroke distance was increased by 51% in 13 anaemic patients ($p<0·001$) and by 43% in 12 pregnant women ($p<0·001$). It was decreased by 14% in 15 hypertensives ($p<0·05$), by 31% in 12 patients with atrial fibrillation ($p<0·01$), and by 43% in 13 patients with cardiac failure ($p<0·001$). Stroke distance was normal in 16 patients convalescing from uncomplicated myocardial infarction.

Measurement of aortic blood velocity and its derivatives by itself, without determination of aortic size, meets the need for a simple non-invasive method of assessing cardiac output.

Early coronary thrombolysis with intravenous BRL 26921: a double blind placebo controlled study

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The efficacy of intravenous BRL 26921, a "protected" streptokinase-plasminogen complex, in producing acute coronary reperfusion was assessed in a double blind placebo controlled trial. Thirty two patients within three hours of the onset of a first transmural myocardial infarction entered the study. Fourteen had anterior and 18 inferior infarcts. Half of each group received active and half placebo treatment. Reperfusion was assessed by coronary arteriography 90 minutes after injection of 30 mg BRL 26921 or placebo (albumin). Coronary vessels were classified as reperfused or occluded without knowledge of the agent administered or the results of coagulation tests. Every patient who received BRL 26921 had patent vessels in the "infarct region" on angiography. All nine inferior infarct patients who received placebo had an occluded right coronary (7) or circumflex coronary (2) vessel. Five of seven patients in the anterior group had total occlusion of the left anterior descending coronary artery. Radionuclide ejection fraction at 10 days was significantly better in the anterior infarct group receiving active treatment (37(7)%) compared with placebo (23(5)%), $p<0·05$. There were two serious but non-fatal bleeding complications in the "active" group and two "late" deaths, both in the placebo group.

Coronary reperfusion following single dose intravenous BRL 26921

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BRL 26921 is an inactive complex of acylated streptokinase and plasminogen with marked fibrin binding capacity. The active compound is produced by deacylation. Previous studies have shown successful coronary artery reperfusion following intracoronary administration within eight hours following acute myocardial infarction. This open study examined its efficacy using the intravenous route. BRL 26921 (30 mg) was given intravenously to 29 patients (23 male, six female, age range 44–71 years) within six hours of acute myocardial infarction (mean 2 h 58 min). Selective coronary arteriography was performed between 60 and 90 minutes following intravenous administration to confirm reperfusion. Anterior descending artery reperfusion occurred in 11 of 12 anterior myocardial infarctions (92%). Vessel patency was confirmed in four of four circumflex and 16 of 17 right coronary vessels in the inferior infarct group (94%). Reperfusion resulted in reversal of the acute electrocardiographic changes of infarct with a reduction in the sum of the ST segment elevation from 16(10) (mean (SD)) to 5(4) mm ($p<0·001$). There was an early peak of creatine phosphokinase release when compared with matched controls. Reperfusion arrhythmias occurred between 30 minutes and 2 hours after intravenous therapy and included idioventricular rhythm, ventricular extrasystoles, and reversal of heart block. There were no associated significant adverse effects.

These results confirm the efficacy of BRL 26921 to obtain reperfusion early in acute myocardial infaction.

Single dose intravenous thrombolysis in acute myocardial infarction: a non-invasive evaluation of a streptokinase-plasminogen activator complex (BRL 26921)

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We report a non-invasive evaluation of the coronary thrombolytic effect of an acylated streptokinase-plasminogen mixture (BRL 26921) administered in a single intravenous dose. Thirty four patients with acute myocardial infarction were investigated; all entered the study within three hours of the onset of symptoms. Sixteen were treated with 20 mg intravenous BRL 26921 followed by a heparin infusion; the remainder formed the control group. Mean creatine phosphokinase activity before and at 12 and 24 hours after treatment was 129(73), 1941(1500), and 1397(814) IU/l respectively. The corresponding values in the control group were 156(19), 1703(852), and 1821(926) IU/l. Two ECG leads were recorded continuously. Computer analysis showed that at two hours ST segment amplitude was 28% of its initial value in the treated patients compared with 79% in the controls. Significant ventricular arrhythmias occurred in 15 treated and 13 control patients; the mean times to the first of these arrhythmias were 142 and 422 minutes in the treated and control groups respectively. Arrhythmias, early creatine phosphokinase peaking, and early reduction of ST segment elevation are accepted markers of reperfusion. All of these were present in 11 of the treated group but in only one of the controls. We conclude that BRL 26921 administered intravenously as in this study can produce coronary thrombolysis.

Angiographic assessment of treatment with intravenous single high dose streptokinase in early severe cardiac infarction

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Fifty consecutive patients (46 male, mean age 56) with early (mean 2 h 50 min pain) severe cardiac infarction (mean Peel Index 14·6) received 1·5 million units streptokinase by intravenous injection over 30 minutes. Coronary artery reperfusion was identified on ECG criteria 20 to 135 minutes (mean 62 min) later with an open infarct-related artery shown by angiography, in 84% of cases. The artery stayed occluded in the remaining 16%. Mean time from onset of pain to coronary reopening was 198 mins. In these severe early infarcts, hospital mortality was 8% (three coronary reocclusions, one mesenteric embolus). There were no haemorrhagic complications needing transfusion within 48 hours of treatment. In those with coronary reperfusion the left ventricular ejection fraction (EF mean 51·4%) was significantly better than in those whose artery stayed closed (EF mean 39·6%) ($p<0·05$), while the numbers with raised left ventricular end diastolic pressure in each group (35% *vs* 67%) were not significantly different ($p=0·12$). Thrombolysis was more likely to fail when patients were treated later (170 min *vs* 212 min, $p<0·05$) after the onset of infarct pain. Reperfusion arrhythmias were frequent but generally trivial, although ventricular fibrillation occurred in one case.

In conclusion, single high dose intravenous streptokinase treatment was followed by coronary reperfusion in 84% of cases and proved free of serious haemorrhagic complications. The earlier the treatment was applied the better the chance of coronary reopening. In hospital mortality may have been improved, and left ventricular function was significantly better in those patients whose affected coronary artery was reopened.

Down's syndrome and complete atrioventricular septal defect: natural history

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Despite advances in surgical technique, repair of the complete atrioventricular septal defect carries a substantial early mortality and the risk of significant ongoing disability due to left atrioventricular valve dysfunction. Any evaluation of the place of surgery as a long term investment for a child with a complete atrioventricular septal defect must take into account the natural (unoperated) history of the condition. At the Brompton Hospital, London, since 1972 we have encountered 62 patients with Down's syndrome and complete atrioventricular septal defect without right ventricular outflow tract obstruction, on whom no surgery has been performed. Operations have been carried out on six patients during this period. Despite medical treatment with digoxin and diuretics, seven died in infancy during the phase of left to right shunting. Nevertheless, after this period mortality and usually morbidity decreased with the advent of pulmonary vascular disease. Actuarial survival at 15 years was 76% and for those who survived to 1 year of age, actuarial survival at 15 years was 87%. These figures compare favourably with published surgical series and it seems likely that short and medium term survival of children with complete atrioventricular septal defect and Down's syndrome will be better without surgery. In the longer term, the life expectancy of patients with Down's syndrome, even without cardiac disease, is curtailed when compared with the normal population.

Cardic malformation in spontaneous abortions

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Although chromosomal abnormalities and external malformations are known to be very common in spontaneous abortions there does not appear to be any information on the frequency of cardiac malformations in such material. The subject was investigated by detailed examination of the hearts of 309 spontaneously aborted fetuses under the age of 24 weeks' gestation, by gross dissection, microdissection, or histological serial sections. Very early specimens, in which cardiogenesis was incomplete, were not included. Forty five instances of cardiac malformations were found (about 15%). There was a bimodal relationship between the incidence of cardiac malformation and both maternal age and parity, and there was a higher incidence in summer conceptions but no apparent association with maternal blood groups. There were more male fetuses and they had proportionately more malformed hearts than the females. There was a marked inverse relationship with fetal age; in early fetuses, under 25 mm (about 9 weeks gestation), cardiac malformations were present in 68%. A wide variety of morphological anomalies was encountered, ranging from simple to multiple and complex; some examples are illustrated. No cardiac malformations occurred in 72 threatened abortions which went to full term delivery.

Patient status five years or more after anatomic correction of transposition of the great arteries

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Between October 1975 and August 1984, 93 patients have undergone anatomic correction of transposition of the great arteries (TGA) at Harefield Hospital. Seventy six patients (82%) survived operation, and 14 have been followed up for more than five years (mean 71 months). Nine patients aged 2 months to 10 years (mean 29 months) had TGA with additional large ventricular septal defect (group A) and underwent a single stage correction. Five patients aged between 4·5 and 21 (mean 9·6) months with simple TGA (group B) had a two stage operation. With a follow up of 65–99 (mean 71) months, there have been two late deaths in group A, one 18 months after operation for progressive pulmonary vascular disease and the other at 3 years of a cerebrovascular accident. The 12 surviving patients are asymptomatic and not on any medication. Holter monitoring has been performed both early and late in all patients. One patient in group B has remained in complete heart block since operation, but all other patients are in sinus rhythm. Routine recatheterisation and angiography have been performed at least once in all patients. One patient had a supravalve pulmonary gradient of 90 mm Hg, 4·5 years after correction and required reoperation. Left ventricular function, coronary artery growth, aortic root size, and anastomotic sites have all been evaluated both angiographically and by sequential echocardiogram. No significant abnormalities were found. Left ventricular ejection fraction was between 55–83% (mean 67%) on angiography. It is concluded that anatomic correction gives satisfactory clinical and haemodynamic results five years or more after operation.

Balloon valvotomy and angioplasty in congenital heart disease: successes and failures

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Balloon valvotomy or balloon angioplasty was successful in avoiding or delaying surgery in 13 of 16 patients with congenital heart disease. In 10 patients aged between 10 days and 7 years balloon pulmonary valvotomy was successful in all but two. In the eight successful cases right ventricular pressures averaged 70·5 mm Hg before and 38 mm Hg after the procedure. Gradients were reduced from an average of 51·5 mm Hg to 15·6 mm Hg. The gradient was not reduced in a neonate with critical pulmonary stenosis and dysplastic valve. In a second patient failure was due to use of too small a balloon (10 mm); the gradient was reduced to 4 mm Hg at a subsequent attempt when an 18 mm balloon was available. Recatheterisation in (so far) five patients at between 13 and 22 weeks demonstrates no significant change (<5 mm Hg) from immediate post valvotomy values in four and a further (15 mm) fall in right ventricular pressure in one patient suggesting that the benefit is retained, at least in the short term. In a patient aged 2½ yrs with complete transposition and previous Mustard's operation balloon angioplasty successful relieved severe obstruction at the lower limb of the baffle; to our knowledge, it is the first use of this technique to overcome this complication. Balloon angioplasty was clinically successful in a patient aged 1½ years with coarctation and abolished the gradient in another aged 3½ years with recoarctation. Finally detachable silicone filled balloons successfully obliterated several pulmonary arteriovenous fistulae causing severe arterial desaturation in a child aged 4 years. Balloon angioplasty failed to achieve dilatation of multiple peripheral pulmonary artery stenoses in a 2 year old. In a 13 year old with double outlet right ventricle and previous Rastelli operation failure to manipulate the catheter into the pulmonary artery frustrated attempts to dilate a severely stenosed homograft valve.

Comparison of ECG gated computed tomography and left ventricular angiography in the measurement of left ventricular function

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Twenty one studies were performed in 19 patients with ischaemic heart disease to compare ECG gated computed tomography with left ventricular angiography in the measurement of left ventricular volumes and ejection fraction. Gated computed tomographic scans each 1 cm in thickness were obtained at 1 cm intervals to image the entire left ventricle during intravenous infusion of contrast medium. End systolic and end diastolic areas were measured at each scan level to obtain the end systolic and end diastolic volumes, and from these ejection fraction was calculated. Angiography was performed in the 40° right-anterior oblique projection, and end systolic and end diastolic volumes were calculated using Kennedy's method. From these the ejection fraction was calculated. Comparison of end diastolic volumes revealed no significant difference between the two methods ($p=0{\cdot}794$). The coefficient of correlation was 0·74. Computed tomography significantly overestimated the end systolic volume ($p<0{\cdot}001$) but the coefficient of correlation was 0·89. Computed tomography significantly underestimated the ejection fraction ($p<0{\cdot}001$) but the coefficient of correlation was 0·76. The results of this study indicate that ECG gated computed tomography is a useful non-invasive method for measuring left ventricular volumes and ejection fraction.

Predicting the outcome of left ventricular aneurysmectomy by phase analysis of equilibrium radionuclide angiography (ERNA)

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Some patients show improvement in left ventricular function following resection of scar tissue (aneurysmectomy) but others do not. The former can be difficult to identify from contrast angiography. Computer processing of ERNA data allows measurement of both the amplitude and timing (phase) of wall movement and is well suited to the identification and quantification of paradoxical wall movement (dyskinesis). We have used this technique to study nine patients selected for aneurysmectomy by conventional angiographic criteria.

Patients were divided into those with dyskinesis (phase $>90°$ and amplitude $>20\%$ of maximum) (group A, $n=4$) and those with akinesis (amplitude $<20\%$) (group B, $n=5$). Before operation group A had a lower global resting ejection fraction than group B ($A=12{\cdot}4(2{\cdot}35)$, $B=22{\cdot}2(1{\cdot}8)$ mean (SEM), $p<0{\cdot}05$) and a higher spread of phase on contractile myocardium ($A=31{\cdot}8°(4{\cdot}9)$, $B=22{\cdot}6°(1{\cdot}8)$, NS). After operation there was an increase in the ejection fraction in group A (29·9(2·1) $p<0{\cdot}05$) but not in group B (21·9(3·0)) and a greater fall in phase spread in group A (17·4(1·35)) compared with group B (20·2(2·6)). The change in ejection fraction correlated with the change in the amount of dyskinesis ($r=0{\cdot}82$, $p<0{\cdot}01$, $n=9$).

The outcome of aneurysmectomy can be predicted from the extent of dyskinesis in the aneurysm but not by the ejection fraction or the function of the contractile segment. This suggests that dyskinesis, demonstrated by combined phase and amplitude analysis of ERNA, may be closer to the definition of a functional aneurysm than that of contrast angiography.

Development of a miniature radiation detector for monitoring left ventricular volumes

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The NaI scintillation probe (nuclear stethoscope) has been traditionally use for monitoring beat to beat left ventricular volumes from technetium-99m labelled blood pool. This instrument cannot be used for continuous monitoring of ambulatory subjects because of its size. Solid state mercuric iodide (HgI_2) has a theoretical advantage in that it has a higher stopping power for gamma rays, for the same volume, that NaI and does not require a photomultiplier tube. We have developed a miniature HgI_2 detector (0·5 mm×65 mm^2) which we have connected via an external amplifier to the computer of a nuclear stethoscope (Bios Inc). In 41 patients, undergoing nuclear probe assessment of left ventricular function, we were able to measure the left ventricular ejection fraction with both detectors. The ejection fraction measurements ranged from 31% to 82%, and over this wide range of values we obtained an equation of: $y=9{\cdot}44+0{\cdot}84x$: $r=0{\cdot}94$ for $n=41$ ($p<0{\cdot}001$). The sensitivity of HgI_2 detector compared with the 51 mm thick NaI detector was 55%. The solid state HgI_2 detector has now been adapted for continuous monitoring of left ventricular time activity curves at the bedside. This development opens up a new field of haemodynamic monitoring of left ventricular function with the possibility of extension to full ambulatory subjects.

ECG gated digital subtraction fine-catheter aortography in evaluation of coronary bypass grafts

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Seven patients with recurrent chest pain have been studied three days to seven months after vein bypass grafting by conventional coronary and graft angiography, and by ECG gated digital subtraction angiography (DSA). DSA involved ascending aortic contrast injection (30 ml iohexol at 15 ml/s) via a 4FG pigtail catheter. Images were acquired in arrested respiration at 0, 300, and 600 ms from the R wave. Grafts were assessed as present or occluded; run off as absent (0), poor (1), moderate (2), or good (3), by two independent observers examining DSA images and angiograms. There were 18 grafts in seven patients, two being shown occluded. This status was correctly identified from DSA by both observers. Of the 16 patent grafts, run-off grading was such that the total score assigned by both observers using conventional angiography was 30/48. Using DSA, run off was scored 29/48 and 27/48 by respective observers. In 6/7 patients visualisation of the native coronary anatomy was also achieved.

In terms of graft patency determination, ECG gated arterial DSA offers 100% sensitivity and specificity and the potential for deployment on an outpatient basis.

Mechanisms of atrial flutter and conversion using atrioversion

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This study evaluated a new technique of electrical stimulation, atrioversion, in the treatment of atrial flutter (AFL). Atrioversion uses a single constant current impulse, with pulse width (mean 250 ms) longer than the flutter cycle length. Rapid atrial pacing is widely used to convert AFL; a review of 22 papers shows that conversion to sinus rhythm occurs in 48% of cases. In 65 cases of AFL, atrioversion produced sinus rhythm in 53%. Selection of a suitable atrial stimulation site affects the success rate. In a type I site, conventional 2 ms pulse width stimuli delivered during flutter produce return cycles which are not fully compensatory; longer return cycles define type II sites. For type I and II sites, conversion rate to sinus was 72% and 48%; the difference was significant ($p<0{\cdot}01$). Conversion for type I sites was higher than for rapid atrial pacing. In five patients, the common form of flutter was converted to the uncommon form, with different P wave axis, by delivering extrastimuli; in six cases, type I responses were found at different atrial sites, separated in activation time by long enough to rule out an ectopic focus. These results lead us to conclude that AFL is due to a macrore-entry circus movement. With careful selection of atrial site, atrioversion has a high success rate in the conversion of atrial flutter.

Abnormalities of the peripheral circulation and respiratory function in patients with severe heart failure

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To investigate the peripheral circulatory and respiratory abnormalities which occur in patients with heart failure we have measured forearm and calf blood flow and calf venous tone, before and after upright exercise, and respiratory gas exchange during exercise in a group of 26 patients with severe heart failure. Compared with a group of normal subjects the patients had reduced limb blood flow at rest and the response of limb blood flow to upright exercise was also abnormal. The patients developed a smaller increase in calf blood flow after exercise ($p<0{\cdot}001$) and also a smaller reduction in blood flow in the non-exercising forearm ($p<0{\cdot}001$). There was a significant correlation between the maximum exercise duration of the patients and calf blood flow both after exercise ($r=0{\cdot}642$, $p<0{\cdot}01$) and at rest ($r=0{\cdot}526$, $p<0{\cdot}02$). The patients were also venoconstricted at rest and after exercise ($p<0{\cdot}01$). Compared with another group of control subjects the patients had a higher minute ventilation during exercise ($p<0{\cdot}03$) and a reduced oxygen consumption ($p<0{\cdot}005$). This latter suggests the early development of anaerobic metabolism during exercise.

A measurement of limb blood flow and respiratory gas exchange are useful non-invasive ways of assessing patients with severe heart failure.

Ambulatory ST segment monitoring: the mechanisms and pathophysiology of nocturnal myocardial ischaemia

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The role of ambulatory ST segment monitoring and the incidence, mechanisms, pathophysiology, and therapy of nocturnal angina were investigated. The sensitivity (70%) and specificity (97%) of ambulatory ST monitoring in detecting coronary disease ($n=100$) was similar to exercise testing but the patients' history of pain had a poor correlation with the frequency of ambulatory ST changes. Nocturnal resting ST changes occurred in 15% of patients; the majority had severe coronary artery disease. Analysis of momentary changes demonstrated that heart rate increases preceded ST depression in the majority of nocturnal episodes in patients with coronary disease ($n=5$). Polygraphic sleep studies ($n=10$) showed that these increases in heart rate were a result of arousal, bodily movement, rapid eye movement (REM) sleep, or apnoea during sleep. Detailed pathological examination of coronary arteries showed no anatomical differences between patients with and without nocturnal ST segment changes and spasm causing total luminal occlusion could not occur in the arteries. Reduction of basal heart rate with atenolol ($n=15$) reduced the frequency ($p<0{\cdot}01$) of nocturnal angina when compared with pindolol, which did not reduce resting heart rate owing to its partial agonist activity. Revascularisation with coronary artery bypass grafting ($n=46$) reduced the frequency of both daytime and nocturnal ST changes.

Thus an increase in myocardial oxygen demand is important in the precipitation of nocturnal resting myocardial ischaemia in patients with coronary artery disease and its reduction produces significant relief in daytime and nocturnal ischaemia.

Improvement in exercise induced ST segment depression early after myocardial infarction

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Forty five male patients with a mean age of 53 years (range 36–67) underwent maximal treadmill exercise testing a mean of 8 days after their first uncomplicated transmural myocardial infarction (MI) when taking no cardiovascular medications. A 12 lead ECG was recorded during each minute of exercise, and directly measured brachial arterial blood pressure was recorded. ST segment depression of >1 mm 0·08 s after the J point constituted a positive response. Twenty three patients developed a positive ECG response during their initial exercise test. The mean (SD) maximal heart rate for these patients was 127(18) beats/min and increased to 139(14) beats/min at week 8 ($p<0{\cdot}001$). Exercise time increased from 6·7(2·1) mins to 9·4(3·9) mins ($p<0{\cdot}001$) and maximal rate pressure product (RPP) from 172(33) to 218(46)

($p<0{\cdot}001$). Mean ST segment depression at maximal exercise decreased from 1·9(0·8) mm at week 1 to 1·1(0·6) mm at week 8 ($p<0{\cdot}01$) with a corresponding fall in exercise induced ST segment elevation in reciprocal leads from 1·6(1·1) mm to 1·0(1·2) mm. Six patients with a positive response during the first study did not show a positive response during the second study despite achieving a higher workload. For the 16 patients with a positive ECG response on both occasions heart rate at the onset of 1 mm ST segment depression increased from 110(12) beats/min to 121(14) beats/min ($p<0{\cdot}01$), RPP from 150(24) to 184(28) ($p<0{\cdot}01$), and exercise time from 3·9(1·3) mins to 6·4(2·4) mins ($p<0{\cdot}001$) between the two studies.

These data suggest that exercise induced ST segment depression may decrease during the early weeks following myocardial infarction, which may account for some of the observed differences in the prognostic significance of ST segment depression at this time. The timing of exercise testing after myocardial infarction may be of fundamental importance.

Exercise testing following myocardial infarction in patients under 55 years: a test of limited value?

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ST segment depression or angina or both during post myocardial infarction exercise testing is reported reliably to predict the extent of coronary artery disease. As such information is important in the management of young patients following myocardial infarction we have studied 100 consecutive patients under 55 years (range 32–54 years, mean 46·6 years) surviving an acute myocardial infarction. They had treadmill exercise tests using a modified Bruce protocol at three weeks (submaximal) and six weeks (maximal) after infarction. During exercise testing 16 lead precordial maps were recorded in addition to standard 12 lead ECG's. All patients had coronary angiography. Forty patients had single vessel disease and 60 patients multivessel disease. Thirty three (55%) patients with multivessel disease had a positive exercise test (angina, ST depression $\geqslant$1 mm or blood pressure fall $\geqslant$20 mm Hg) six weeks following infarction compared with 22 (37%) at three weeks ($p<0{\cdot}05$) using the standard 12 lead ECG. The 16 lead precordial map did not improve detection of multivessel disease. The sensitivity, specificity, and predictive value of a positive six week postinfarction exercise test for multivessel disease was 55%, 70%, and 73% respectively. Twenty five (81%) of the 31 patients who had angina during the exercise test six weeks postinfarction had angina on follow up compared with 14 (20%) of the 69 who did not ($p<0{\cdot}001$).

Thus exercise testing at six weeks following myocardial infarction in patients under 55 years is of limited value in detecting multivessel disease but is a reliable predictor of angina on follow up.

Reproducibility of ischaemic abnormalities resulting from maximal exercise tests performed predischarge and six weeks after infarction

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Symptom limited treadmill exercise tests were performed predischarge and six weeks after myocardial infarction (MI), without complications, in 64 patients (mean age 55 years) to assess the reproducibility of abnormalities of prognostic value. There was a significant lack of reproducibility among those patients with angina ($p<0{\cdot}005$) and an abnormal blood pressure (BP) response ($p<0{\cdot}05$). ST segment depression and elevation and ventricular arrhythmias were relatively reproducible. There was a significant increase in the frequency of an ischaemic response from the early to the later test ($p<0{\cdot}01$) associated with a significantly longer exercise duration ($p<0{\cdot}001$) and a greater mean maximal heart rate ($p<0{\cdot}001$) and heart rate-systolic BP double product ($p<0{\cdot}001$). Eight patients were not retested at six weeks. Six of these had complications after leaving hospital; two reinfarcted, one of whom died, and four had unstable angina. All six patients had had an abnormal predischarge test ($p<0{\cdot}05$).

We conclude that the majority of patients who develop immediate complications after infarction can be identified with a predischarge exercise test. Because exercise induced ST segment depression and elevation are reproducible, patients who develop these abnormalities at the predischarge test do not, for prognostic reasons, need retesting at six weeks. Angina and an abnormal BP response, however, are highly variable, and in these patients a repeat test may be useful.

Coronary morphology and ventricular function in patients with positive exercise tests following myocardial infarction

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Coronary morphology and left ventricular (LV) function were investigated in 76 survivors of acute myocardial infarction with positive predischarge exercise tests. Patients were selected by ST depression in a 12 lead treadmill test (73 patients) or by an abnormal exercise blood pressure (BP) response (3 patients). Coronary anatomy and LV performance were determined at catheterisation. Multiple vessel disease was demonstrated in 60 of the 73 (82%) patients with ST abnormality remote from the site of infarction. A single locus of ST abnormality based on ECG lead groupings was present in 46 patients. Dual loci were present in 27 patients, of whom 25 had multiple vessel disease (7 double vessel disease, 15 triple vessel disease). Seventy eight of the 101 (77%) loci of ST abnormality corresponded to coronary arteries with significant stenosis, and 65 (83%) of those diseased vessels served LV segments with normal wall motion. Twenty seven loci of ST abnormality corresponded to normal vessels. In 18 of these 27, exercise induced ST elevation in alternate loci or arteriographic collateral circulation or both suggested a possible coronary steal mechanism. An abnormal BP response was elicited in 17 patients, all of whom had multivessel disease compared with 24 patients with a BP increase >20 mm Hg, of whom nine had single vessel disease. Mean LV ejection fraction was significantly lower in the former group (0·45(0·04)) compared with the latter (0·58(0·04); p<0·01).

A positive predischarge exercise test conferred a high risk of multiple vessel disease. The locus of ST abnormality was related to disease in individual vessels which supplied preserved LV segments. Abnormal BP response indicated multiple vessel disease and impared global LV performance.

Painless myocardial ischaemia: sequence and magnitude of left ventricular volume changes

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Left ventricular volume (precordial counting of technetium-99m labelled blood pool) and the electrocardiogram were continuously recorded in 12 patients with angina at rest during 11 spontaneous (two painful) and 12 ergometrine induced (nine painful) attacks of acute myocardial ischaemia, characterised by ST segment elevation in 13 (four painful) and ST segment depression in 10 (seven painful). All ischaemic episodes were accompanied by progressive left ventricular dilatation, reduction of stroke volume and ejection fraction. These changes preceded the onset of diagnostic ST segment change and, when present, the onset of pain. The total duration of ventricular dilatation was greater in painful episodes than in painless episodes. Rate of change of volume was less in ergometrine induced episodes than in spontaneous episodes and less in those with ST segment depression than in those with ST segment elevation. Nevertheless, there was no significant difference in rate of volume change between painful and painless episodes. The maximum change in end systolic volume, end diastolic volume, stroke volume, and ejection fraction was 133(50)% (mean (SD)), 38(8·0)%, −28(17)%, and −32(8·7)% respectively for painful episodes. It was 110(27)%, 26(12)%, −25(12)%, and −25(6)% respectively for painless episodes.

Asymptomatic ST segment changes are accompanied by the typical left ventricular volume changes of acute myocardial ischaemia but differences in magnitude or initial rate of ventricular dilatation do not appear to be sufficient to explain the occurrence of pain.

Implications of the routine use of beta blockade after myocardial infarction in England and Wales

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Long term beta blockade after myocardial infarction has been suggested significantly to improve one year survival. The purpose of this study is to estimate the effect and cost if this policy were applied nationally. During 1981, in England and Wales, 100 360 patients were admitted to hospital following acute myocardial infarction. Of these, 75 240 were discharged. Two trials have shown a mortality for treatment groups of 6·8% (timolol) and 3·6% (propranolol) in the first year after infarction. The corresponding placebo groups had mortalities of 10·7% and 6·0%. This has been interpreted as a 30% reduction in mortality. Alternatively, this could be seen as an improvement from an average 92% survival without treatment to 95% with beta blockade. Nationally, there is a potential saving of 2300 lives. This contrasts with a national mortality, in 1981, of 107 000 from myocardial infarction. For each patient the cost of one year's treatment with timolol (10 mg twice daily) is £77·53 and with propranolol (80 mg thrice daily) £69. Treatment of all 75 240 survivors would cost £5 833 060 with timolol and £5 190 430 with propranolol. The cost per life saved would be £2540 for timolol and £2260 for propranolol. In practice fewer lives could be saved because both studies indicated that 18% of infarct survivors had contraindications to treatment with beta blockade.

It is concluded that in England and Wales approximately 1900 lives might be saved in the first year after infarction at a cost of about £4 553 000.

Can good risk patients with acute myocardial infarction be discharged after four days?

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Reducing the length of hospitalisation of patients with acute myocardial infarction would release resources for other patient care. We report a randomised study to determine if very short stay (four days) versus long stay (seven days) management of patients with low risk affects the outcome at three months looking at (*a*) mortality and (*b*) cardiac events (death and non-fatal reinfarction) as end points. Non-invasive prognostic index identified 45·5% of patients to be low risk. Data were examined by "intention to treat" and by explicitative analysis. Using "intention to treat" analysis, 187 patients were allocated to four day discharge and 177 to seven day discharge. Mortality at three months was 8·0% and 4·0% and cardiac events 9·1% and 5·6% respectively. By explicitative analysis, 137 patients were discharged on the fourth day, and 155 on the seventh day. Mortality at three months was 5·8% and 1·3% respectively. Cardiac events occurred significantly more often in the early discharge patients (10·5%) than in the late discharge group (3·2%).

Heart rate variability during acute myocardial infarction: relation to ventricular fibrillation

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Complex autonomic effects occur during acute myocardial infarction, may relate to pathogenesis of ventricular fibrillation (VF), and may be reflected by patterns of RR interval variability. Detailed analysis has been performed of electrograms from 14 cases of acute myocardial infarction developing VF and 15 cases of acute infarction (six anterior, nine inferior) without VF. Electrograms were processed from tape by computer in five minute segments to determine RR intervals, sequential RR interval differences (excluding ectopic beats), and calculate 10th to 90th centile sample ranges. Distinctive patterns of RR variability observed include (*a*) sinus arrhythmia, (*b*) oscillation at about 0·1 Hz, (*c*) bursts of sinus tachycardia (1–2 minutes), with or without ventricular arrhythmias, and (*d*) absence of any visible oscillation. Abolition of patterns (*a*) and (*b*) was observed after administration of atropine. During the five minute period preceding VF, the prevalence of pattern (*d*) was significantly greater (nine cases/14) than was found in comparable 5 min periods (10/74) in 15 cases not developing VF ($p<0{\cdot}001$) and mean RR interval shorter (680(38) ms *vs* 750(22) ms. RR difference range was greater in inferior (49(6) ms) than anterior (20(2) ms) infarction ($p<0{\cdot}001$). Although mean RR interval was more prolonged during inferior (803(24) ms, $p<0{\cdot}05$) than anterior infarction (726(22) ms) no correlation was found between RR difference range and heart rate ($r=0{\cdot}09$).

Results suggest that the heart may be subject to parasympathetic influences which can be independent of heart rate during acute inferior infarction and that withdrawal of vagal tone with enhanced sympathetic activity may immediately precede VF.

A comparison of bepridil with amiodarone in the conversion of established atrial fibrillation

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While conventional drug treatment of established atrial fibrillation rarely reestablishes sinus rhythm amiodarone converts approximately 40% of patients. Bepridil, introduced for angina, has both fast and slow channel blocking properties and possesses antiarrhythmic properties. We have compared bepridil with amiodarone in 18 patients with poorly controlled and established atrial fibrillation (mean ventricular rate >100/min; duration >1 month). The ventricular rate was assessed at rest and during a standard treadmill exercise test (Naughton protocol) performed weekly over three weeks on bepridil (200, 400, and

600 mg/day) and at two and four months on amiodarone (400 mg/day). During bepridil 9/14 patients returned to sinus rhythm, while during amiodarone 4/13 converted. In the 10 patients who received both agents sequentially bepridil converted six and amiodarone four. In those patients remaining in atrial fibrillation amiodarone reduced the ventricular response more at rest (baseline: 145(38), amiodarone: 101(6), bepridil: 117(32) (mean (SD)); on exercise control was similar. The ventricular rate in atrial fibrillation was not further slowed by increasing bepridil above 200 mg/day, but more patients returned to sinus rhythm (200 mg, n=2: 400 mg, n=6: 600 mg, n=9). In 8/9 patients, returning to sinus rhythm on bepridil, the QTc was >440 ms. This prolongation of the QTc was dose related, and in two patients on 600 mg/day the return to sinus rhythm was associated with a QTc of >600 ms and torsade de pointes which degenerated into ventricular fibrillation in one.

While bepridil proved useful for the conversion of established atrial fibrillation, its effect on the QTc and the associated ventricular arrhythmias are likely to restrict its use and dosage.

Clinical use of intravenous flecainide for acute onset of tachyarrhythmias

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Intravenous flecainide (2 mg/kg) was given during acute onset tachycardias to 75 patients. Twelve had atrial flutter and 12 atrial fibrillation (including three with pre-excitation). Thirty two had junctional arrhythmias (atrioventricular (AV) re-entrant tachycardia in 20, AV nodal tachycardia in 12) and 19 had ventricular tachycardia. In the following, ventricular rates (1 standard deviation from the mean in beats per minute) before and after flecainide are shown in brackets. Atrial flutter was terminated in 2/12 patients (112(14) to 87(7); $p<0.001$). Atrial fibrillation was stopped in 11/12 cases (159(11) to 121(9); $p<0.05$). Atrioventricular tachycardia was reverted in 17/20 patients (188(34) to 142(27); $p<0.001$). Intra-AV nodal tachycardia was stopped in 10/12 cases (175(36) to 134(20); $p<0.001$). Ventricular tachycardia was reverted in 15/19 patients (176(13) to 115(14); $p<0.01$). In those with junctional tachycardias, termination was in the retrograde limb (accessory pathway or "fast" AV pathway) in 25 and anterograde limb (AV node) in only two. Four had proarrhythmic effects. One, with AV nodal tachycardia, developed ventricular fibrillation, and another with ventricular tachycardia degenerated into fibrillation; both had received other antiarrhythmic drugs, and two patients with atrial flutter developed fast ventricular rates. All four responded to electrical therapies. Minor side effects included oral parasthesiae, transient dizziness, and visual blurring.

Flecainide is an effective and relatively safe drug for the termination of recent onset paroxysmal atrial, junctional, and ventricular tachyarrhythmias of all types except atrial flutter.

D-sotalol—the clinical electrophysiological effects of a new class III antiarrhythmic agent

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The clinical importance of drugs with class III antiarrhythmic activity has been established. Sotalol, in addition to its beta blocking action, has class III activity, thought to be a property of the dextroisomer. We have studied the electrophysiological effects of the pure dextroisomer (d-sotalol) in five patients undergoing investigation for arrhythmia; three had paroxysmal ventricular tachycardia, one had AV nodal re-entry tachycardia, and one paroxysmal atrial flutter. D-sotalol 0·75 mg/kg was administered intravenously over 10 minutes during sinus rhythm after baseline electrophysiological measurements had been obtained; these included 90% repolarisation time derived from a monophasic action potential recording. The electrophysiological variables were re-evaluated 10–20 minutes after the end of infusion. There was a small decrease in mean heart rate from 88 to 80 beats/min, prolongation in surface QTc interval (428(15) to 442(16) ms (mean (SD)), but no change in intracardiac conduction intervals. AV nodal refractoriness was unchanged. Prolongations in both atrial (208(9) to 227(15) ms) and ventricular (228(12) to 250(24) ms) effective refractory periods occurred together with a lengthening of the 90% repolarisation time (260(12) to 284(24) ms). In two patients with VT inducible prior to d-sotalol, VT could not be induced after drug administration: in the other patient non-sustained VT (cycle length 220 ms) was induced prior to the infusion, slower but sustained VT (cycle length 260 ms) being induced afterwards.

This study is the first to demonstrate the class III antiarrhythmic action of d-sotalol; the absence of an

AV nodal action suggests that the immediate effects are not achieved by beta adrenoceptor antagonism. The electrophysiological profile suggests that d-sotalol will be an important alternative to amiodarone for the management of arrhythmias.

Xamoterol, an oral agent for the treatment of sinoatrial disease?

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Xamoterol (Corwin) is a highly selective beta_1 adrenoceptor antagonist with 45% intrinsic sympathomimetic activity; this combination suggests a role in the treatment of sinoatrial disease. Ultilising a randomised double blind crossover study over four weeks with placebo run-in and washout, xamoterol 200 mg twice daily was compared with placebo. At the end of each week, patients were assessed by a semi-quantitative symptom checklist and Holter monitoring outside hospital. The tapes were analysed blind for the hourly RR interval distribution, the number of pauses $>1{\cdot}74$ s, the longest pause, and the presence of atrial arrhythmias. Twelve patients (eight men, four women; aged 50 to 79 years, mean 64·8 years) were studied. Eleven were symptomatic; nine were referred for consideration of permanent pacing. Eight had atrial tachycardias in addition to sinus bradycardia or atrial pauses. Xamoterol reduced the range of RR intervals over 24 hours. The drug was of clinical benefit in 10 patients. Six showed a reduction in the number and maximum duration of pauses. Three reported symptomatic improvement associated with an increase in mean heart rate. The other patient also had an increase in mean heart rate but was unable to describe her symptoms. Six patients are now on long-term therapy. One of the 12 patients showed no improvement; another with paroxysmal atrial flutter deteriorated.

The drug treatment of sinoatrial disease can be assessed outside hospital in a wide range of patients. In many patients xamoterol could provide simple but effective therapy.

Effect of successful percutaneous transluminal coronary angioplasty on myocardial perfusion and function

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Thallium 201 scintigraphy (Tl 201) and technetium angiography (Tc-99m) were performed on 19 patients before and six weeks after successful treatment by percutaneous transluminal coronary angioplasty (PTCA). The degree of reversible myocardial ischaemia at exercise and rest was assessed on Tl 201 scintigrams using a four point ischaemia score (0, normal, 3, severe abnormality) with images obtained in four standard views and the myocardium divided into five anatomical segments. Successful dilatation was achieved in 23 vessels in the 19 patients. Symptomatic improvement was maintained in 17 patients at six weeks and effort tolerance improved from 97(6) to 111(6) J ($p<0{\cdot}02$). Reversible ischaemic score (RIS) in the whole group improved from 3·0(0·9) to 0·6(0·2) ($p<0{\cdot}05$). Left ventricular ejection fraction (LVEF) at rest remained unchanged. LVEF at exercise increased from 0·40(0·03) to 0·52(0·02) ($p<0{\cdot}001$). Seven patients (group 1) had a significant ($p>0{\cdot}05$) increase in exercise LVEF. The RIS in this group prior to PTCA was 7·8(1·8) whereas in 12 patients without improvement in exercise LVEF the RIS was 0·8(0·03) ($p<0{\cdot}001$). There were no differences in either groups in numbers of vessels treated or site of lesion.

This study showed that improvement in left ventricular systolic function following successful PTCA was more likely in patients with substantial degrees of reversible ischaemia before the procedure.

PTCA in unstable angina: comparison with stable angina

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Unstable angina is a recognisable clinical entity with a significant risk of subsequent myocardial infarction and death. Percutaneous transluminal coronary angioplasty (PTCA) was performed in 25 patients presenting with unstable angina and the early and late results analysed in order to assess its efficacy in the treatment of this condition. Results were compared with a similar group of 25 patients with stable angina in whom PTCA was also performed. The incidence of single, double, and triple vessel disease was identical in each group. Technical success was achieved in 23 out of 27 (85%) attempts in the unstable group and in 14 out of 27 (52%) attempts in the stable group ($p<0{\cdot}05$). Vessel occlusion occurred in nine patients overall, necessitating emergency bypass surgery in four. Evidence of myocardial infarction was found in three (12%) patients in each group, and one patient in the unstable group subsequently died. Twenty patients in the unstable group have been followed up for a mean period of 7·6 months. Nineteen patients are symptom free while one (5%) has recurrent angina.

These results compare favourably with published reports on unstable angina treated medically or surgically and demonstrate the effectiveness of PTCA in this condition.

Clinical effects of prolonged balloon inflation during coronary angioplasty and their moderation by intracoronary nitroglycerin

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Prolonged balloon inflation time (30–60 s) has been shown to improve results of coronary angioplasty, but the extent of the ischaemia so produced has not been well defined. We studied the haemodynamic and electrocardiographic effects of prolonged inflation during angioplasty of the proximal left anterior descending coronary artery in 29 patients, before and after administration of 0·2 mg nitroglycerin (NTG) through the distal balloon catheter port. There were no significant changes in heart rate or aortic pressure during balloon inflation, with or without NTG. Before NTG, baseline pulmonary wedge pressure was 11·1(6·2) mm Hg and after NTG was 7·4(4·3) mm Hg ($p<0{\cdot}001$). Wedge pressure at 60 s inflation was 18·3(7·4) mm Hg before NTC and 14·5(6·8) mm Hg after ($p<0{\cdot}001$). The time to an increase in wedge pressure ≥ 5 mm Hg was 31·6(13·9) s before and 40·8(16·3) s after the drug ($p<0{\cdot}005$). The time to appearance of ST segment elevation or depression $>0{\cdot}1$ mV in lead I or aVL was 25·2(12·1) s before NTG and 34·5(16·2) s afterward ($p<0{\cdot}001$). Six patients with an increase in wedge pressure ≥ 5 mm Hg during balloon inflation had no detectable electrocardiographic alterations.

In conclusion, pulmonary wedge pressure rises in response to balloon inflation during coronary angioplasty and is a more sensitive indicator of ischaemia than aortic pressure or electrocardiographic changes in standard leads. Intracoronary nitroglycerin delays the appearance of the rise in wedge pressure and limits its extent; it also delays the onset of ischaemic ST segment changes. Monitoring of wedge pressure and administration of intracoronary NTG improve the safety of employing an extended inflation period during coronary angioplasty.

Successful percutaneous coronary angioplasty in totally occluded coronary arteries

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In a consecutive series of 70 procedures, percutaneous transluminal coronary angioplasty (PTCA) was performed in eight patients with total occlusion. Occlusion occurred up to eight months between diagnostic angiography and PTCA and was associated with increased anginal symptoms but no Q wave infarction. The procedure was successful with no complications in seven patients, with angiographic evidence of vessel patency up to nine months later. One patient had successful recanalisation of the obstructed vessel but required emergency bypass grafting following PTCA of another vessel. All patients had symptomatic improvement and four were pain free at follow up between three and 14 months. Thallium 201 scintigraphy before and after PTCA showed regression of fixed defects in four patients and normalisation of defects in two.

In conclusion, coronary artery occlusion unassociated with a Q wave infarct can be treated by PTCA with substantial clinical benefit and no increased risks.

Should angioplasty be attempted for occluded vessels?

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In the course of 107 consecutive angioplasty procedures in 103 patients, an attempt was made to recanalise mechanically an occluded vessel on 15 occasions. Two patients had suffered an acute myocardial infarct with vessels that were presumed to have occluded within the previous two hours. In these individuals recanalisation was successful and antegrade flow re-established with prompt relief of pain and reversal of ECG changes. Thrombus was not observed in the affected vessel and streptokinase was not used. Follow up angiography revealed continued patency of the vessels without significant obstruction. In 13 chronically occluded vessels, guide wire passage was successful in five with balloon passage in three and successful dilatation in one. At restudy the only successfully dilated vessel had asymptomatically reoccluded. In the group as a whole the primary success rate for dilatation of stenoses was 79% with evidence of myocardial damage occurring in seven, of which five developed Q wave infarction. One patient was treated by immediate surgery. There were no deaths. No complications occurred in relation to attempted recanalisation of occluded vessels.

In sharp contrast to dilatation of stenoses, recanalisation of chronically occluded vessels with currently available techniques is unsuccessful, uncomplicated, and unrewarding.

Outcome of early surgery following coronary angioplasty

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Nineteen (27%) of 69 patients undergoing angioplasty underwent immediate coronary surgery, six planned for continuing angina after failed angioplasty. The remaining 13 were operated upon because of complications: they were dissection in four, occlusion in five, continuing severe spasm in two, tamponade in one, and in one other detachment of a guide wire tip. The angioplasty was for a lesion in the anterior descending in eight (62%) patients, the right in four (31%), and the circumflex in one (8%). This was a similar distribution to the 56 patients without complications. There was one early postoperative death due to extensive anterior myocardial infarction, and there was ECG evidence of new infarction in three others. Nuclear left ventricular angiograms were performed in 16 of the 18 patients surviving immediate surgery after a mean of 27 months. These were compared with the cineangiograms performed prior to attempted angioplasty. Only two patients showed evidence of a new left ventricular wall motion abnormality, the remaining 14 having normal left ventricular contraction both at rest and after a maximal bicycle exercise.

Prompt surgery after angioplasty complications is usually successful with good symptomatic relief and without left ventricular damage. The incidence of important surgical complications in these low risk patients is, however, high. These are not always included in reported angioplasty series being "lost" in the "emergency surgery group."

Are changes in left ventricular function during exercise related to the extent of coronary artery disease? A study using first pass radionuclide angiography with gold-195m

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To examine if sequential changes in left ventricular ejection fraction during exercise could quantify the extent of coronary disease, 25 patients underwent first pass radionuclide angiography with gold-195m ($t\frac{1}{2}$ 30·5 s). Seven patients had normal coronaries (group A), 11 had single or double vessel disease (group B), and seven had triple vessel disease (group C). Ejection fraction was measured at rest, three minutes, six minutes, peak, immediately after, and 2 minutes after exercise. Ejection fractions did not fall in group A during exercise. In group B it fell from 58(10)% (mean (SD)) at rest to 51(10)% at three minutes, and 47(10)% at peak (both $p<0·05$ *vs* rest); after exercise it rose to 64(8)% ($p<0·05$ *vs* rest). In group C, ejection fraction fell from 57(12)% at rest to 42(9)% at three minutes, and 35(8)% at peak (both $p<0·05$ *vs* rest). It did not rise above rest after exercise. Seventy per cent of group C and 45% of group B had abnormal exercise responses at three minutes, and all group C and 75% of group B were abnormal at peak. The rate of change of ejection fraction from rest to peak was +0·6(0·9)%/min for group A, −2·1(1·7)%/min for group B ($p<0·01$), and −4·7(2·7)%/min for group C ($p<0·001$ *vs* group A, $p<0·05$ *vs* group B), but there was overlap between groups A and B and groups B and C.

In conclusion, (*a*) falls in left ventricular ejection fraction at submaximal exercise help identify patients with severe coronary disease, (*b*) the rate and duration of ejection fraction depression are related to extent of coronary disease but the degree of overlap precludes definite anatomical classification in individuals, and (*c*) in patients with single or double vessel disease, rapid or sustained falls in ejection fraction may suggest similar amounts of muscle at risk as in triple vessel disease.

Three dimensional quantification of left ventricular wall motion by ECG gated blood pool emission tomography

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In equilibrium radionuclide ventriculography, imaging of the left ventricle is restricted principally to a single projection to avoid overlap with the right ventricle. This problem can be overcome using the new technique of ECG gated blood pool emission tomography, in which information from multiple projections is reconstructed into tomographc sections through the intracardiac blood pools. This study establishes a simple method for displaying the three dimensional data so obtained, determines a normal range for ejection fraction in all regions of the left ventricle, and compares wall motion in abnormal subjects with that determined by *x* ray contrast ventriculography. Regional ejection fraction was plotted on a colour coded circular image, in which the apex was represented in the centre, the base around the circumference, and all other parts of the ventricle were represented in between. The image was divided into 15 segments, and normal segmental ejection fraction was defined as within two standard deviations of the mean in a group of 10 normal subjects. In 25 subjects with coronary artery disease, motion of the anterior, apical, and inferior walls agreed in every case with the right anterior oblique contrast ventriculogram, but in 12 of these, the three dimensional ejection fraction image showed abnormal septal motion in addition. In all 12 there was disease of the left anterior descending coronary artery.

ECG gated blood pool emission tomography thus provides an accurate quantitative assessment of left ventricular wall motion in three dimensions and has significant advantages over conventional planar techniques.

Measurement of valvular regurgitation by first pass radionuclide angiocardiography

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A novel technique is described for the measurement of valvular regurgitation. After bolus administration intravenously of 740 MBq of 99m technetium pertechnetate activity is sampled over the lung and left ventricle and flow calculated from the resulting indicator dilution curves. In mitral or aortic regurgitation tracer passing to and fro across the valve is sampled more than once in the ventricle but not the lung. The area under the ventricular, but not the pulmonary, curve will be overestimated, and thus flow will be underestimated. This effect should be proportional to the degree of regurgitation. In 24 normals the ratio of pulmonary to left ventricular flow (Pf/LVf) had a gaussian distribution with a mean value of 1·0 and standard deviation (SD) of 0·1. The mean Pf:LVf ratio of 14 further subjects without valvular regurgitation but with reduced left ventricular ejection fraction (0·45–0·17, mean 0·35) was also unity. All values differed 2SD from the mean of the normals. All of 20 subjects with valvular regurgitation did, however, manifest abnormally low Pf:LVf values. The distribution in these subjects was skewed to the left, reflecting varying degrees of valvular regurgitation with a modal value of 0·7 and a range of 0·4–0·8.

The ratio Pf:LVf can be used to quantify valvular regurgitation. It is simple to perform, non-invasive, and independent of impaired left ventricular contraction.

Magnetic resonance cine imaging of the human heart

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A new method which allows five magnetic resonance sections to be produced at the same anatomical level at predetermined points in the cardiac cycle has been developed. This has been achieved by modifying an ECG gate spin echo sequence. A further five sections can be interleaved by repeating the sequence and employing a gating delay. The five to 10 sections produced are then displayed in a cine mode. A Picker International superconducting magnet operating at 0·26 Tesla has been used to collect the anatomical data. The cine sequence has been obtained on an independent IGE system. Five volunteers and four patients have been studied. By using the coronal plane for cine display direct comparison can be made with left ventricular angiography. Myocardial thinning, localised areas of dyskinesia, and valvular motion are clearly visualised. Subjective estimates can be made of left ventricular ejection fraction and further work is in progress to determine objective measures of cardiac function. A signal observed in the great vessels and pulmonary circulation should permit further study of blood flow.

Nuclear magnetic resonance imaging in hypertrophic cardiomyopathy and hypertension

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Proton nuclear magnetic resonance (NMR) permits visualisation of cardiac structures, and with measurement of the spin-lattice relaxation time (T_1) tissue characterisation may be possible. We have explored the capability of calculated T_1 images, obtained from inversion recovery and saturation pulse sequences using a low field (0·08T) resistive magnet to differentiate between normal and hypertrophied hearts. Eleven patients with hypertrophic cardiomyopathy diagnosed either by echocardiography or by cardiac catheterisation were compared with 11 age matched volunteers and 11 patients with hypertension and electrocardiographic evidence of left ventricular hypertrophy (LVH). The ratio of septal to LV thickness in patients with LVH measured by NMR was 0·8(0·2) (SD) and by echocardiography 0·9(0·3). In patients with hypertrophic cardiomyopathy the ratio was 1·5(0·8) and 1·6(0·6) respectively. Septal area in volunteers was 2·7 cm^2 compared with 4·6 cm^2 and 6·2 cm^2 for patients with LVH and hypertrophic cardiomyopathy. Corresponding areas for LV free wall were 3·7, 6·3, and 6·1 cm^2. For all groups septal T_1 was higher than free wall T_1.

NMR allows two dimensional estimation of septal and free wall mass without the limitations of echocardiography. Gated NMR will improve accuracy and precision and allow more subtle differences in T_1 to be observed.

Magnetic resonance imaging of the human heart

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ECG gated and non-gated magnetic resonance studies have been performed in 22 volunteers and 30 patients with proven cardiac disease. The contours of the ventricular and atrial chambers together with major vessel morphology can be identified on non-gated images. Image quality improved significantly during ECG gated studies and allowed identification of many additional features. The transverse axial plane permitted evaluation of ventricular and atrial size and of myocardial thickness. The morphological features of each chamber and their associated valves were clearly identifiable. The mid-coronal plane approximates best to the right anterior oblique left ventricular angiogram. Using this plane, particularly in the cine mode, it has been possible to identify localised areas of wall thinning and to assess regional wall motion. It is concluded that non-gated magnetic resonance imaging is a useful method of examining the great vessels and may be used to identify all cardiac chambers. ECG-gated magnetic resonance, however, significantly improves image quality enabling the internal morphology of the heart to be examined in considerably greater detail. Areas of myocardial thinning are readily detectable and estimates of left ventricular wall motion can be made. Magnetic resonance imaging was performed on a Picker International superconducting magnet operating at 0·26 Tesla.

Ventricular arrhythmia surgery based on a new mapping

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In 17 patients with recurrent medically intractable life threatening ventricular tachycardia or ventricular fibrillation, arrhythmia surgery was based on electrogram mapping in sinus rhythm. The patients were aged 32 to 65 years; 16 had had a myocardial infarction (three weeks to 15 years previously) and one had a "normal" heart. In the ischaemic patients the mean ejection fraction was 25% (range 13–44%). Epicardial and endocardial maps (53 and 36–48 points respectively) were obtained in sinus rhythm in all patients. Mapping during the arrhythmias was possible in only seven patients. Fragmentation (electrogram duration >100 ms) in sinus rhythm was used to identify areas for endocardial resection. Fragmentation always extended beyond any aneurysm resection line but was not always associated with visually abnormal endocardium. In the one patient with a "normal" heart, fragmentation was present throughout the left ventricle and almost all the left ventricular endocardium was resected. Resection was supplemented by coronary artery bypass grafting in 10 patients, and aneurysmectomy in 12 patients. The operative mortality was 30% (four pump failure, one infection). Durng a mean follow up of 13·8 months (range 2 months to 3·2 years) there have been no arrhythmia recurrences or late deaths.

Thus effective surgery for refractory ventricular tachycardia and ventricular fibrillation can be based on electrogram characteristics determined during sinus rhythm. Arrhythmia surgery is now possible in situations where peroperative arrhythmia maps are unobtainable (for example, ventricular fibrillation). Morever, as this technique is applied in haemodynamically stable conditions, the risks of preoperative myocardial damage may be minimised.

Exercise electrophysiology study of arrhythmias

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Eighteen patients with tachycardias have been investigated with programmed stimulation studies during erect maximum exercise. Fifteen patients had leads placed in the right atrium, coronary sinus, or right ventricle and two leads were used in three patients. In 12 cases an active fixation screw-in lead was used in the right atrium. All leads were inserted percutaneously via a subclavian vein. In 12 of the 18 (67%) patients the exercise study revealed arrhythmias which could not be induced at rest even following atropine. These arrhythmias included atrial fibrillation (seven), re-entry tachycardia (six), atrial flutter with block (one), and ventricular fibrillation. PR interval changes were also disclosed. In one patient with Wolff-Parkinson-White syndrome atrial fibrillation induced at rest was well tolerated but during exercise caused syncope. There were no complications from the studies. In 10 of the 18 cases the management was changed as a result of the exercise findings. In many patients it is no longer adequate for electrophysiological studies to be performed only at rest.

Atrioversion—conversion of atrial flutter in man using a long constant current pulse

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This study evaluated a new technique of electrical stimulation, atrioversion, in the treatment of atrial flutter (AFL). Atrioversion uses a single constant current impulse, with pulse width (mean 250 ms) longer than the AFL cycle length. Rapid atrial pacing is widely used to convert AFL; a review of 22 papers shows that conversion to sinus rhythm (SR) occurred in 48% of cases, and that a long duration of flutter or digitalisation or both lowered the success rate of rapid pacing. Atrioversion was used to treat 65 cases of spontaneous AFL in 59 patients (46 male, 13 female, mean age 54 years). Ten were converted using one to three conventional coupled extrastimuli (nine to SR, one to atrial fibrillation (AF)). In the remaining 55, atrioversion produced sinus rhythm in 28 (53%). AF occurred in 20 (36%), and in six (11%) AFL persisted. Nine patients spontaneously returned to sinus rhythm from AF. SR was regained immediately in 37 of the 65 (57%) cases, and overall in 47 (72%). The most important factor affecting success rate was selection of a suitable atrial stimulation site. When conventional ms pulse width stimuli delivered during AFL produce return cycles which are not fully compensatory, a type I response is seen; longer return cycles define type II sites. For type I and II sites, immediate conversion to SR was 72% and 48%; the difference was significant ($p<0{\cdot}01$). It is presumed that a type I site is closer to the origin of the flutter. Duration of flutter and digoxin were not shown to significantly affect conversion rate. Atrioversion has a high success rate in converting atrial flutter to sinus rhythm and, with optimal catheter positioning, is more successful than rapid atrial pacing ($p<0{\cdot}015$). Its usefulness in other arrhythmias is being evaluated.

Repetitive ventricular responses in at risk patients following myocardial infarction: relationship to left ventricular function

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Although ventricular function is accepted as the principal factor in determining survival following myocardial infarction, it remains to be established whether additional prognostic information may be obtained by studying rhythm abnormalities provoked by ventricular electrical stimulation. Such responses were studied within one month of infarction in 90 consecutive patients considered "at risk" because of a positive early submaximal exercise test. A positive electrical response was defined as 4 or more spontaneous ventricular beats after delivery of either single or extrastimuli at diminishing intervals to the right ventricle in sinus rhythm or at paced cycle lengths of 600 and 500 ms. Eight of 48 patients with anterior and 11 of 42 patients with inferior infarcts had positive responses. These 19 patients with a positive response had a similar mean ejection fraction (54·7(18·0)% *vs* 46·9(17·6)%) and regional ventricular wall motion score (19·7(4·6) *vs* 19·8(6·0)) compared with the 71 patients with a negative response (14 of whom had an ejection fraction of <35%). Significant abnormalities on 24 hour ECG monitoring were found in five of 19 patients with a positive response compared with seven of 71 patients with a negative response. Four of 70 patients followed for a minimum of three months (mean 7–9 months) have died. All four patients had positive electrical responses, but only one had an abnormal 24 hour ECG. Nevertheless, these four patients had a lower mean ejection fraction, (26·6(12·4)% *vs* 59·0(14·1)%) and higher mean wall motion score (24·0(6·9) *vs* 20·8(5·1) compared with those patients with positive electrical responses who have survived. This suggests that positive electrical responses are not related to ventricular function and may indicate a poor prognosis in those patients with severe ventricular dysfunction.

Effects of iloprost, a stable prostacyclin analogue, on exercise tolerance and platelet aggregation in patients with stable angina pectoris

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Prostacyclin and its analogues combine in one molecule two properties—coronary dilatation and anti-platelet action—which seem extremely promising for the treatment of stable angina pectoris. Accordingly we assessed the effects of iloprost, a chemically stable compound which has been shown to have prostacyclin mimetic activities, on exercise tolerance and platelet aggregation in 24 patients with effort angina and proven critical ($\geqslant$70%) coronary artery disease. Upright bicycle ergometer testing (25 W increments every 2 min) was performed during iloprost (6 ng/kg per min) or placebo infusion and 30 and 60 minutes later, using a crossover randomised single blind protocol. Samples for measurements of adenosine diphosphate (ADP) induced platelet aggregation were obtained before and throughout the study. Compared with placebo, intravenous iloprost administration consistently ($p<0·001$) prolonged exercise duration (mean (SD): 511(142) *vs* 436(146) s) and time to onset of significant (0·1 mV) ST segment depression (368(140) *vs* 285(122) s). Also, angina occurred at a higher ($p<0·001$) heart rate (138(11) *vs* 130(13) beats/min) and rate pressure product (26·2(3·0) *vs* 23·5(2·9)$\times 10^3$U). Similar differences in exercise duration and time to onset of ST segment depression were observed when comparing placebo with iloprost 30 minutes after infusion. Changes in platelet aggregation paralleled those in exercise duration and a marked decrease in ADP induced platelet aggregation during exercise was found concurrently with iloprost infusion (by 78(12)%) and 30 minutes later (by 52(16)%). No significant differences in exercise tolerance and platelet aggregation were observed between placebo and iloprost 60 minutes after their infusions.

We conclude that (*a*) iloprost administration improves exercise tolerance in patients with stable exertional angina pectoris; and (*b*) improvements are independent of changes in the major determinants of myocardial oxygen demand and are associated with markedly reduced platelet aggregation. Benefits in exercise tolerance might be due to diminished release of vasoactive platelet derivatives and increased myocardial perfusion.

Effects of placebo on indices of exercise induced myocardial ischaemia—an objective analysis

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It is known that placebo can influence the frequency of anginal attacks favourably, but there is no clear consensus on exercise tolerance. This has considerable implications for the ethics of placebo periods in clinical trials of antianginal drugs. We have analysed the effects of placebo in 150 patients (135 male, 15 female) aged 42–75 years with stable exertional angina pectoris who had participated in single and double blind studies. Multistage treadmill graded exercise testing (modified Chung's protocol), using online computer analysis of the electrocardiogram (Marquette CASE I), was performend after the patients had been on no treatment for at least two weeks and after two weeks of oral treatment with placebo three times a day. The leads monitored were CC5 and CM5 and recorded as 25:1 computer averaged complexes. The tests were performed at a controlled temperature between 20°C and 24°C on the same equipment between 09·00 and 11·00. Although 20% of the patients showed subjective improvement, the objective measurements were not altered by placebo. The mean (SEM) exercise time untreated was 6·0(0·2) minutes and with placebo was 6·1(0·2) minutes (NS). Similarly, the 1 mm ST depression time was 4·0(0·2) minutes with no treatment and 4·1(0·2) minutes after placebo (NS) and the resting and maximal heart rates were 74(1) and 124(1) beats/min respectively untreated and 73(1) and 122(1) beats/min respectively after placebo treatment (NS). The placebo failed to show any effect on maximum ST segment depression. These results question the need for placebo control in antianginal drug trials which use exercise testing for the evaluation of effect.

A modified Bruce protocol compared with the original

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The Bruce protocol is widely used in exercise ECG testing for the recognition of myocardial ischaemia. It has the disadvantage of taking a considerable time to perform, and some patients stop prematurely before the age predicted heart rate has been achieved. Such tests are inconclusive. In an attempt to overcome these difficulties, the stages of the Bruce regimen were reduced from three minutes to one minute. A comparison was made of 25 patients undergoing the full Bruce protocol (B) and the same patients doing a modified exercise test (A) with similar increments of speed and gradient but progressing at one minute intervals. At least one hour elapsed between the two tests. Half the patients did A first and half B. Group 1 ($n=17$) were on beta blocking drugs and group 2 ($n=8$) were not. All patients who had a positive exercise test on B also had a positive test on A. The mean heart rate of group 1 rose from 57·2 to a maximum of 116·5 beats/min on A and from 61·3 to 109·6 beats/min on B. Group 2 maximum heart rate rose from 72·3 to 155·6 beats/min on A and from 69·3 to 138·6 beats/min on B. The difference is not statistically different ($p>0{\cdot}01$). The mean maximal systolic blood pressure response was not significantly different between the two protocols. The mean ST depression at maximum heart rate was 1·95 mm (range 0·5–2·6) on regimen A and 2·18 (0·6–2·9) on B in group 1 and 0·73 (0·1–1·7) on protocol A and 0·76 (0·1–1·9) on B. The average duration of exercise on protocol A was 4·9 mins and on B 8·6 mins. These results show that the modified protocol (A) is entirely comparable to the conventional Bruce protocol and much less time consuming.

Elevated diastolic blood pressure response to exercise testing when coronary artery disease is suspected: an indication of severity

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Our objective was to evaluate the significance of a rising diastolic blood pressure during exercise. One hundred and two consecutive patients with a history of chest pain underwent maximal symptom limited treadmill stress testing and coronary angiography. The diastolic blood pressure response to exercise was evaluated independently of ST segment change and systolic blood pressure (SBP). In the presence of a normal systolic blood pressure response an increase in DBP of 15 mm Hg on at least two determinations during the same stage of exercise was considered abnormal. Of the 61 patients with normal DBP response, the ST segment change was positive for ischaemia in 25. Seven of these had three vessel coronary artery disease. Of the 38 patients with an abnormal DBP response, 27 had a positive exercise ECG for ischaemia. Eleven patients had a negative exercise ECG. Of these, one had left main stem disease, seven had three vessel disease, and the remaining three had two vessel disease. In these 11 patients the diastolic blood pressure response to exercise was abnormal. ST segment analysis showed that patients with abnormal diastolic blood pressure had more ST segment depression than those with a normal diastolic blood pressure response (1·48(0·17) *vs* 0·93(0·16), $p<0{\cdot}05$). In addition there were significantly more patients developing angina (78% *vs* 31%) at a significantly reduced exercise time in the group of patients with an abnormal diastolic blood pressure when compared with those showing a normal response (5·3(1·8) *vs* 7·6(1·7) mins, $p<0{\cdot}001$).

Thus an abnormal diastolic blood pressure response to a maximal symptom limited treadmill stress test is a useful additional indicator of the severity of coronary artery disease and may be of special clinical value when the ST segment response is normal or borderline.

Long term follow up of ST segment reciprocal change in acute myocardial infarction: correlation with exercise testing and coronary angiography

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Our objective in this study was to evaluate the significance of ST segment "reciprocal" changes defined as >1 mm in the ECG leads other than those reflecting acute myocardial infarction. Eighty five consecutive uncomplicated cases of acute myocardial infarction were studied prospectively with maximal symptom limited treadmill stress tests at two weeks and coronary angiography at six weeks post infarction. Forty six patients had inferior, 34 anterior, and five true posterior infarction. Of the 51 patients with reciprocal changes, 45 (88%) developed exercise induced ST segment depression in areas remote from the infarction zone. At angiography all 45 were shown to have stenoses >70% in at least two major vessels.

Four patients had negative exercise ECGs and were subsequently shown to have single vessel coronary artery disease subtending their infarct, and the remaining two patients had a false negative treadmill result. Of the 34 patients without reciprocal changes, 21 (62%) had a negative treadmill stress test associated with single vessel disease, five had a positive stress test and multivessel disease, and one had a false negative stress test. The remaining seven patients had ST segment elevation without Q wave formation in the reciprocal areas. Of these, six had positive stress tests and multivessel disease and one had a negative test and single vessel disease to the infarct area. At follow up (36 months) of the 51 patients with reciprocal ST segment change, 36 became symptomatic and 29 of these underwent coronary bypass surgery. By contrast, only seven of the 34 patients without reciprocal ST segment change developed symptoms and three of these underwent coronary revascularisation. Reciprocal ST segment depression at the time of acute myocardial infarction may identify patients with significant coronary artery disease and when positive appears to be as reliable as early post infarction treadmill stress testing in predicting the underlying coronary anatomy. Nevertheless, when negative, treadmill testing provides valuable diagnostic information.

The role of ambulatory ST segment monitoring in clinical practice

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The role of 48 hour ambulatory monitoring was investigated in 100 consecutive patients with chest pain undergoing stress testing and arteriography. Patients were off antianginal medication. Nineteen per cent of patients with normal coronaries had reversible ST changes (specificity 77%), of whom only 3·8% had proven coronary spasm. ST changes occurred in 70% of patients with coronary artery disease; 73% had positive stress tests. Three vessel disease was detected more efficiently than single vessel disease, but poor left ventricular function was more often associated with the absence of ST changes ($p<0{\cdot}01$). Ninety six per cent had episodes of ST depression and 4% also had ST elevation. The frequency, duration, and magnitude of episodes were greater in patients with more severe disease and lower exercise tolerance in whom the heart rate at the onset of ST depression tended to be lower. Nocturnal ST changes occurred in 15% of patients (three vessel disease or left main stenosis), but a third did not complain of any rest pain. No correlation existed between the history of pain and either the severity of coronary artery disease or frequency of ST changes. Only 76% of patients with frequent pain (>1/day) had ST changes, whereas 66% of patients with infrequent pain (<1/week) also had changes in 48 hours of monitoring. Painful ST changes (33% of total) occurred with similar frequency in patients with varying severity of coronary artery disease. Thus the history was not a sensitive indicator of the frequency of underlying ischaemia (ST changes). If therapy is to be tailored to the type of angina (rest/exertional) ambulatory ST monitoring is desirable.

Exercise testing and arrhythmia monitoring predicts triple vessel disease post infarction

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In order to investigate the associations between blood pressure (BP) response, time to onset of ST segment depression during exercise, and subsequent coronary anatomy routine exercise stress testing was undertaken in 93 patients three weeks post infarction. BP was measured at rest and post exercise. Thirty seven (40%) patients had a positive test and underwent coronary angiography. The percentage rise in systolic BP on exercise was 27(2)% for those with a negative test, and 27(4)% and 23(6)% for those with single and double vessel disease respectively. In marked contrast, those with triple vessel disease only increased BP by 5(2)% ($p\leq0{\cdot}005$). Onset time to 1 mm ST depression was 4·6(0·5) min and 4·2(0·8) min for single and double vessel disease compared with 2·1(0·4) min for those with triple vessel disease ($p\leq0{\cdot}01$). In 65 patients, 24 hour ECG taping was undertaken eight days post infarction. The mean Lown score was 1·9(0·2) in those with a negative test, 3·0(0·4) for a positive test ($p\leq0{\cdot}01$), 1·3(0·3) for single vessel disease, 2·6(0·7) for double vessel disease, and 3·2(0·3) for triple vessel disease ($p\leq0{\cdot}01$).

Triple vessel disease post infarction relates to early onset of ST depression, poor exercise BP response, and significantly increased ventricular arrhythmias.

Prognostic value of non-invasive investigations in the management of the post myocardial infarction patient

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The ability of non-invasive techniques to predict further cardiac events and multiple vessel coronary disease was investigated in 46 apparent low risk survivors of acute myocardial infarction. Exercise electrocardiography (ETT), rest/exercise thallium-201 (Tl–201) scintigraphy, and rest/exercise radionuclide angiography (RNA) were performed prior to hospital discharge. At investigation, half were beta-blocked and thereafter all patients were given prophylactic beta blockade. Coronary arteriography was performed at three months post discharge. During a mean follow up of 12(4) months, 12 patients (26%) experienced cardiac events (recurrent myocardial infarction, three patients; angina pectoris, 11 patients; coronary surgery, six patients). No patient died during the follow up period. Ten of the 12 were identified by Tl–201 scintigraphy (reversible image defect) or positive ETT, and seven displayed abnormal left ventricular exercise reserve. The predictive accuracy of Tl–201, ETT, and RNA for cardiac events was 87%, 76%, and 57% respectively and was not influenced by beta blockade. Tl–201 specificity for cardiac events (88%) exceeded that of ETT (76%) and RNA (56%; $p<0{\cdot}01$). The predictive accuracy of Tl–201, ETT, and RNA for multivessel disease was 89%, 70%, and 80% respectively. Nevertheless, arteriographic multivessel disease, although 100% sensitive, was a non-specific predictor (52%) for subsequent cardiac events.

Thus Tl–201 scintigraphy appeared to be the technique of choice for the assessment of patients following myocardial infarction both in terms of subsequent cardiac events and predicting multiple vessel disease. The accuracy of the technique was not reduced by beta blockade.

Does intravenous loading with amiodarone hasten the appearance of an electrophysiological effect?

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The significant delay between starting oral amiodarone and the demonstration of an antiarrhythmic effect is an important problem when treating "malignant" arrhythmias. We have assessed whether intravenous loading will accelerate the appearance of an electrophysiological change. Eleven patients were randomly allocated to either intravenous or oral loading with amiodarone, given over 30 hours. A bipolar electrode was placed at the right ventricular apex and at least 24 hours later the baseline effective refractory period determined. Six patients received intravenous amiodarone by a constant infusion (0·65 mg/kg/h): three into an antecubital vein and three into a central vein. Five patients received oral amiodarone (0·85 mg/kg/h) given as divided doses (10 mg/kg/12 hourly). The refractory period was determined at a constant cycle length (S_1-S_1) of 500 ms at baseline and then serially at 6, 12, 18, and 30 hours after starting amiodarone. At the same times amiodarone and desethyl amiodarone serum concentrations were measured. After oral amiodarone the refractory period did not increase until 30 hours ($p=0{\cdot}022$); with intravenous loading the refractory period was significantly increased at 18 hours ($p=0{\cdot}032$) and at 30 hours showed further lengthening ($p=0{\cdot}0043$). Two patients receiving intravenous amiodarone experienced nausea, while the three patients in whom the intravenous amiodarone was given into a peripheral vein developed thrombophlebitis necessitating a change of infusion site. One patient receiving oral amiodarone felt faint without a change in blood pressure.

While intravenous loading hastens the onset of an electrophysiological effect there is still a significant hiatus during which protection against arrhythmias is likely to be inadequate.

What is "controlled atrial fibrillation"?

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Ambulatory 24 hour ECGs were recorded in 66 patients with chronic atrial fibrillation judged clinically to be adequately controlled. Recordings were analysed to assess fastest and slowest heart rates in each hour, duration of pauses, and the nature and frequency of ventricular arrhythmias. Maximum heart rates occurred during the day in all patients, ranging from 84 to 188 beats per full minute, and exceeding 150 beats/minute in 18 patients (27%). Slowest heart rates ranged from 34 to 82 beats/minute, occurred at night in 63 patients (95%), and were less than 40 beats/minute in 12 patients (18%).

Pauses longer than 1·5 s occurred at night in 59 patients (89%) and during the day in 35 (53%). Pauses longer than 2·0 s were seen in 44 patients (67%) and 13 (20%) had pauses lasting between 3·1 and 4·0 s. Only two patients had no ventricular arrhythmias. More than 500 ventricular extrasystoles per day were recorded in 38 patients (58%). Twenty patients (30%) had other ventricular arrhythmias including frequent couplets, bigeminy, and ventricular tachycardia. In 59 patients taking digoxin fastest heart rates, nocturnal bradycardia, length of pauses, and ventricular arrhythmias all correlated poorly with serum digoxin levels.

Thus in patients with clinically "controlled" atrial fibrillation ambulatory ECG recordings may show marked variations in heart rate despite apparently appropriate suppressant therapy. Nocturnal bradycardia and asymptomatic pauses of up to 4 s duration may occur without digoxin toxicity and do not warrant cardiac pacing. Ventricular arrhythmias are common without digoxin excess and are probably due primarily to the underlying heart disease.

Ambulatory monitoring of atrial electrograms

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One of the limitations of conventional ambulatory ECG monitoring is the difficulty in reliably detecting the P wave. Using a two channel ambulatory ECG recorder, we monitored the endocardial atrial electrogram obtained with a temporary bipolar screw-in lead in 18 patients and with a conventional temporary bipolar electrode positioned in the coronary sinus in two patients. A surface ECG lead (CM5) was recorded simultaneously on the second channel. Clear electrograms were obtained in all cases; initial mean amplitude 1·38 (range 0·7–2·8) mV with final amplitudes of 1·1 (range 0·4–2·2) mV. A mean initial injury current of 0·76 (range 0·3–2·1) mV was seen in 17/18 patients with the screw-in lead falling to 0·54 (range 0–2·4) mV after 24 hours. In nine patients with accessory AV conduction pathways, spontaneous arrhythmias were not seen during the recording period but the electrode was used to initiate and terminate re-entry tachycardia under different autonomic settings. Tachyarrhythmias were seen in nine patients: four, atrial, four, ventricular, and one, Coumel. In all cases, useful or diagnostic information, not available from the surface ECG, was provided by the atrial electrogram. The electrode was used to terminate atrial flutter in two patients, Mobitz II AV block was seen in one patient in whom the electrode did not provide additional information whereas in another patient with apparent AV dissociation on the surface ECG the atrial electrogram revealed PR alternans during sinus rhythm. There were no displacements or complications. We conclude that in selected patients with tachyarrhythmias, ambulatory monitoring of the atrial electrogram is a safe and useful addition to the technique of ECG monitoring offering an occasional therapeutic option.

Ventricular tachycardia misdiagnosed as supraventricular tachycardia

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The differential diagnosis of broad QRS complex tachycardias can be difficult and despite well defined criteria misdiagnosis of ventricular as supraventricular tachycardia with aberration is still common. Over a five month period in two institutions we have seen 21 instances of this problem. The history and 62 12 lead ECGs during ventricular tachycardia (VT) were reviewed to see if strict application of existing criteria would have enabled earlier correct diagnosis. In 16/21 patients there was a past history of myocardial infarction, 9/21 had a documented LV aneurysm, and 10/21 had previous ECG evidence of complex ventricular ectopy. VT was haemodynamically stable in 14/21. In 10/21 patients and 34% of ECGs diagnostic features of VT were present (AV dissociation, fusions, captures). QRS width was >140 ms in 58% of episodes. Left bundle branch block QRS type was seen in 18%, right bundle branch block type in 31%, and indeterminate in 51%. 1:1 retrograde conduction was seen in 8%, left axis deviation (<−45°) in 37%, and precordial QRS "concordance" in 26%. In 4/21 patients two or more QRS types during separate episodes were noted. In 19/21 verapamil was given intravenously on at least one occasion and never with success. In 17/21 patients intracardiac studies proved a ventricular origin. Careful analysis of ECGs could have resulted in correct diagnosis in most cases with consequent important influences on subsequent management. Other features which appeared to contribute to misdiagnosis included reluctance to make a diagnosis of VT, misconception that VT always causes circulatory collapse, failure to take into account past history, and unwillingness to change an established diagnosis. These patients highlight the importance of careful review of all data before VT is excluded and inappropriate management instituted.

Death and damage after multiple DC countershocks

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Many patients who receive multiple defibrillator shocks have a poor prognosis. Is this due to the underlying disease or to adverse effects of the shocks? Greyhounds (25·4(0·79) kg), with a heart weight comparable to that of man, were anaesthetised with pentobarbitone (30 mg/kg) and received either 1, 5, or 10 synchronised transthoracic shocks of 400 J at intervals of 30 s from a Lown-type defibrillator. Acute mortality increased with increasing numbers of shocks (one shock 0/6; five shocks 8/18; 10 shocks 12/17: $p<0·025$). The terminal ECG showed unco-ordinated irregular atrial and ventricular activity, progressing within minutes to asystole. Electron and light microscopy at this time showed no reproducible lesions in the contractile apparatus. Three days after the shocks the hearts of five survivors in each group were excised. These were sliced and incubated in 1% triphenyltetrazolium chloride (TTC). The one shock group showed little damage (0·004(0·004) G; mean (SEM)), few associated ECG changes, and minimal ventricular ectopic activity during the three day survival. The five shock (7·2(2·0) G) and 10 shock groups (13·1(1·8) G) showed considerable damage with transmural right ventricular involvement, acute injury changes in the ECG and a late sustained ventricular tachycardia of the Harris type which was maximal at 24 hours following the shocks. Optimised first shock effectiveness is essential to minimise the clinical need for 5–10 shocks, associated here with gross cardiac damage and acute mortality.

Haematological and tissue effects of high energy ablation

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Endocardial ablation has been performed with catheter electrodes on the His bundle or in the coronary sinus. Application of the technique to ventricular tachycardia (VT) foci could involve the use of electrodes in the left ventricle (LV). We have therefore investigated the tissue and haematological effects plus gas production when high energies are delivered via standard USCI bipolar catheter electrodes (BE). A flexible plastic bag filled with 300 ml of fresh citrated blood was suspended in a tank of normal saline. The distal electrode of the USCI BE was immersed in the blood and 40×100 J delivered. Gas produced was collected and analysed and the blood assessed for haemolysis. Tissue experiments were performed on the left ventricle from freshly killed pigs. Myocardial temperature and pressure changes were recorded at various depths during delivery of 400 J impulses to the endocardium. Forty 100 J shocks produced 0·5 ml of gas. Analysis showed release of hydrogen and reduction of oxygen. There was haemolysis of 3% of haemoglobin. The pressure measured was approximately 20 psi, 2·5 cm from the electrode at a depth of 0·5 cm from the endocardium, falling to 5 psi on the epicardium. Corresponding temperature rises were 0·13°C and 0·03°C respectively.

The small quantity of free gas, slight haemolysis, and pressure and temperature changes do not suggest that it is unsafe to apply high energies to the left ventricle endocardium in man.

Origin of late potentials defined by ECG signal averaging

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Late potentials obtained by signal averaging of surface ECGs are thought to reflect myocardial depolarisation outside the normal duration of the QRS. Their precise origin is, however, uncertain. We compared the signal averaged ECGs of 11 patients with direct recordings of epicardial and endocardial electrograms at surgery. Surgery was: coronary grafting in two patients, endocardial resection for arrhythmias in six patients, aneurysmectomy in three patients. The timing, duration, and morphology of electrograms from 53 epicardial and 36 endocardial sites were compared with the averaged surface ECG obtained before or during surgery. Late potentials were recorded in seven patients (five with arrhythmias, two without). In six of the seven patients the timing of epicardial electrogram fragmentation was closely correlated with the timing of surface late potentials. Late potentials were seen if three or more epicardial sites showed fragmentation (>100 ms). The seventh patient has QRS widening between averaging and surgery. Surgical excision of sites of fragmentation abolished late potentials. The four patients without late potentials (two with arrhythmias) showed no epicardial fragmentation. The relationship between endocardial fragmentation and late potentials was less clear. In three patients, the duration of endocardial fragmentation (more than three sites) exceeded that of epicardial fragmentation but was not reflected as late potentials.

We conclude that late potentials represent fragmented delayed ventricular activation occurring predominantly in the epicardial myocardium.

Physiological pacing in children

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Active children with symptomatic heart block require pacing at constantly high rates to allow for the variable demand. Physiological pacing, therefore, would appear ideally suited for this group of patients but there are specific technique problems. We implanted dual chamber pacemakers in four patients aged between 11 and 13 years. All had symptomatic complete heart block which was congenital in two and followed surgical repair for congenital heart disease in the other two. The technique differs from implantation in adults in allowing lead length for growth. The association of congenital heart disease may enlarge the right atrium and encourage early lead displacement, which occurred in two of our patients. Associated systemic venous anomalies may limit access to endocardial pacing. Two of our patients had previous demand units and have observed significant improvement in activity with the physiological system. The other two, paced for the first time, have also noticed other benefits in addition to the cessation of syncopal attacks. Two patients required reprogramming, one initially because of exercise induced angina and later for pacemaker mediated re-entry tachycardia.

Physiological pacing in children appears to produce significant benefits particularly during exercise, predominantly due to the rate response and perhaps to the contribution from atrial transport.

His bundle ablation using lower energies and an active fixation electrode

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Endocardial ablation of the His bundle has previously been attempted using high energies and standard catheter electrodes. We have attempted to reduce energy requirements by use of an active fixation electrode. Five patients (four men, one woman) aged 48–69 years were studied. Four had paroxysmal atrial fibrillation (PAF) and one had tachycardias due to dual AV nodal pathways (DAVN). Pre-ablation, AV node Wenckebach occurred at 150–220 beats/min (mean 176/minute), VA Wenckebach 160–200 beats/minute (mean 172/minute). A temporary pacing electrode was inserted into the right ventricle, and a Vitatron Helifix (VH) electrode introduced via the right femoral vein and positioned to obtain the maximal His bundle deflection. Five shocks (1×25 and 4×50 J) were delivered via the VH at one minute intervals. The other output of the defibrillator was connected to a paddle placed on the posterior chest wall. Blood for cardiac enzyme estimation was then obtained. All patients developed complete heart block (CHB) immediately postablation; the two patients in atrial fibrillation reverted to regular sinus node activity. Complete heart block persisted in two patients and was intermittent in one. All required permanent pacemakers. Two patients had first degree AV block and right bundle branch block one month postablation (mean AV Wenckebach 120/minute, VA 100/minute). All patients remained asymptomatic. Maximum creatine phosphokinase values occurred one hour postablation with no significant rise in creatine phosphokinase MB.

Therefore His bundle ablation can be safely and successfully performed using an active fixation electrode and lower energies. This method may prove valuable for ablation of other cardiac sites involved in tachyarrhythmias.

Effect of antiarrhythmic drugs and atrial pacing on atrial repolarisation using high gain surface electrocardiography

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High fidelity (0·16 to 30 Hz), high gain (x 1000 to x 10

000) ECGs (leads I, II, and III) were recorded from 29 supine patients with heart block. The P wave duration (atrial depolarisation), the length of Ta wave (atrial repolarisation), and the total interval were measured from five non-conducted atrial events. Progressively increasing the atrial pacing rate from 80 to 150 beats/min resulted in a linear reduction of the PTa interval from 430 to 280 ms (rho=0·66, slope=0·29). This was due largely to shortening of the Ta component. Atropine (0·02 mg/kg) shortened the PP interval (748(96) to 581(69) ms, $p<0·001$) and the PTa interval (386(29) to 355(99) ms, $p<0·01$). Propranolol (0·15 mg/kg) prolonged the PP interval (699(82) to 826(99) ms, $p<0·001$) but did not alter the PTa interval (405(19) to 405(37) ms, NS). Neither disopyramide (2·0 mg/kg) nor flecainide (2·0 mg/kg) altered the PP interval (732(77) to 678(68) ms (NS) for disopyramide and 724(91) to 704(52) ms (NS) for flecainide) but both prolonged the PTa interval (394(14) to 429(13) ms, $p<0·001$ for disopyramide and 400(20) to 433(11) ms, $p<0·001$ for flecainide). The increase in PTa after flecainide was largely due to P wave lengthening (P: 104(11) to 129(18) ms, $p<0·001$; Ta: 296(19) to 304(19) ms, NS) whereas after disopyramide most of the PTa increase was due to Ta changes (P: 102(8) to 109(7) ms, NS; Ta: 292(10) to 320(14) ms, $p<0·001$). Atropine shortened both components of the PTa (P: 102(12) to 95(12) ms, $p<0·001$; Ta: 284(22) to 260(31) ms, $p<0·001$) and propranolol had no effect (P: 104(5) to 105(7) ms, NS; Ta: 301(20) to 300(39) ms, NS).

In heart block both P and Ta waves can be reliably measured and the effects of pacing and drugs on the atrial myocardium can be assessed. The results are consistent with cellular electrophysiology and similar to the effects on the human ventricle.

Quantitative comparative analysis of argon and Nd-YAG laser radiation of normal and atheromatous arterial walls

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In some cases submitted for percutaneous transluminal balloon angioplasty the stenosis is too narrow to be traversed with the balloon or guide wire or both. An alternative approach is to use fibre-optically guided laser radiation to vaporise transluminally some of the occluding atheroma. The continuous wave Nd-YAG and argon lasers employ optical fibres and are used clinically. We have quantified the effects of these two lasers on normal and atheromatous arterial wall. Three hundred and fifty five separate craters were made in samples of normal and atheromatous human postmortem aortic wall by pulse durations from 0·1 to 5·0 s of Nd-YAG and argon radiation, of power ranges 5 to 70 W and 1 to 3 W respectively. Crater depths were measured to the nearest 0·05 mm. For both lasers, crater depth was proportional to pulse energy rather than power. With Nd-YAG radiation, to maintain crater depths within 0·8 mm the maximum permissible pulse energy was 12 J for normal and 8 J for atheromatous aortic wall. For smaller crater depths, similar differences in maximum pulse energies were noted between normal and atheromatous aortic wall. Argon radiation did not show similar selectivity for atheromatous aortic wall, the corresponding maximum pulse energies being 1 J for 1 mm crater depth, 0·6 J for 0·6 mm, and 0·2 J for 0·4 mm for both normal and atheromatous aortic wall. Percutaneous transluminal delivery of laser energy to the coronary circulation will require optical fibre core diameters of 200 μm or less. With the argon laser a 200 μm core fibre was used. Nevertheless, the optics of the Nd-YAG laser-fibre interface were such that to transmit power sufficient to produce a predictable effect on the target, a fibre core diameter of at least 400 μm was necessary. Thus although the Nd-YAG's selective effect upon atheroma makes it theoretically preferable to the argon, in practice the optics of the system dictate that the argon laser is likely to be the more appropriate for coronary angioplasty.

Differential transmission spectrometry of normal and atheromatous arterial wall

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For the technique of laser angioplasty to be safe and reliable, the laser energy must not only be direct at, but also absorbed by, atheromatous plaque rather than normal arterial wall. For any given wavelength, the degree of light absorption (and hence vaporisation) which takes place is an inherent physical property of the target; and it is important to know this property (optical absorption) for both atheroma and normal arterial wall. We measured the optical transmission from 450 nm to 800 nm of five samples each of atheromatous and of normal human postmortem aortic wall. With emitting and receiving optical fibres on either side of the sample, chopped white light was passed through the sample into a monochrometer to select wavelengths from 450 nm to 800 nm, whose intensities were measured by a phase sensitive detector. The distance between the emitting and receiving optical fibre tipes could be adjusted and measured by a micromanipulator. In both normal and atheromatous aortic wall the percentage optical transmission varied inversely with thickness of sample and directly with wavelength. For a thickness of 0·9 mm, the optical transmission of normal and atheromatous aortic wall fell from 45% and 22% respectively at 750 nm to 12% and 2·5% respectively at 450 nm. The ratio of the optical transmission per unit thickness of normal aortic wall to that of atheromatous aortic wall was 2:1 from 800 nm to 600 nm, rising to 5:1 at 500 nm.

Thus between 800 nm and 450 nm atheteromatous aortic wall absorbs light more strongly per unit thickness than normal aortic wall, and this effect is most pronounced at 500 nm. Such wavelength-dependent differential optical absorption between normal and atheromatous aortic wall can be used to improve the selectivity and safety of laser angioplasty.

Apolipoprotein gene polymorphisms as markers for atherosclerosis

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A recent report suggests that certain DNA polymorphisms may provide genetic markers for atherosclerosis. We have described a DNA polymorphism at the apolipoprotein A-I/C-III gene cluster, which associates with hypertriglyceridaemia. In view of the importance of these apolipoproteins in high density lipoprotein (HDL) and very low density lipoprotein (VLDL) metabolism, and the relationship between HDL levels and the development of atherosclerosis, we have studied the distribution of this polymorphism in groups of patients with or without angiographically defined coronary atherosclerosis. Leucocyte DNA from Caucasian subjects was digested with the restriction endonuclease Sst-I, Southern blotted and hybridised with a ^{32}P-labelled M13 genomic clone containing sequences coding for apolipoprotein A-I. Restriction fragments hybridising to the apo A-I probe were detected by autoradiography. The polymorphism was revealed by the presence of either a 4·2 Kb or 3·2 Kb restriction fragment. The 3·2 Kb allele is found in 30% of subjects with hypertriglyceridaemia but in less than 5% of controls. The 3·2 Kb allele was found in five of 33 subjects with extensive coronary atherosclerosis, and in two of 34 subjects with normal coronary arteries. These subjects were age and sex matched. The difference in distribution is not statistically significant, yet the possession of the 3·2 Kb allele may still be implicated in the development of coronary atherosclerosis. Further studies are required using other lipoprotein gene polymorphisms to establish their relevance to the development of coronary atherosclerosis.

High density lipoprotein-cholesterol, alcohol intake and ischaemic heart disease

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High density lipoprotein-cholesterol (HDL-C) is regarded as a well established protective factor in ischaemic heart disease. Results from the prospective phase of the British Regional Heart Study, involving 7735 middle aged men, show that low levels of HDL-C are associated with increased risk of ischaemic heart disease but that there is no evidence of a protective effect from higher levels. A critical review of four other prospective studies of HDL-C and ischaemia heart disease suggests that the importance of HDL-C as a protective factor may have been exaggerated. HDL-C concentration is increased by alcohol consumption and this finding is used to support the widely held view that moderate drinking is protective against ischaemic heart disease. Results from the Regional Heart Study confirm the increase in HDL-C concentration with increasing alcohol intake but provide no evidence of any protective effect of alcohol on the risk of major ischaemic heart disease. Overall, results from this study suggest that HDL-C is neither a useful predictor of the risk of ischaemic heart disease nor an important protective factor in ischaemic heart disease in these middle aged British men. There is also no support for the view that moderate drinking may protect against ischaemic heart disease.

Occult coronary artery disease in familial hypercholesterolaemia

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Familial hypercholesterolaemia (FH) is well know as a risk factor for coronary artery disease. We have investigated the presence of coronary artery disease in 60 asymptomatic patients (19 female, 41 male), mean age 40·5 years with FH and a normal resting ECG. FH was diagnosed on standard criteria: fasting total cholesterol $>$7·3 mmol/l and low density lipoprotein $>$4·4 mmol/l, a family history of early arterial disease in a first degree relative, and/or presence of xanthelasma, early corneal arcus, or tendon xanthoma. Other major risk factors for coronary artery disease (diabetes, smoking, hypertension, and obesity) were present with expected frequency relative to the general population or were under-represented. Patients were investigated by 16 lead chest wall mapping during and after exercise. Thirty patients (50%) had positive tests, and, of these, 19 underwent coronary angiography. Significant narrowing ($>$50%) in one or more vessels was present in 18. During four years of follow up coronary events occurred in 16 of the 30: 14 had angina with 11 proceeding to coronary artery bypass grafting and two had a myocardial infarct. There were no such events in the 30 patients with negative exercise tests. This group had a lower total cholesterol: 7·9(2·1) mmol/l (mean (SD)) *vs* 9·3(1·6) mmol/l (p$<$0·01) and a higher density lipoprotein: 1·29(0·23) mmol/l *vs* 1·5(0·25) mmol/l (p$<$0·05), but showed no difference in any other risk factor when compared with the 30 patients with positive exercise tests. This study demonstrates the ability of the exercise test to detect occult coronary artery disease and to predict subsequent major coronary events in patients with FH. The increased risk appears to be related solely to the level of the lipoprotein abnormality.

Underestimation of coronary arterial stenosis by arteriography

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Postmortem perfusion-fixation of coronary arteries at physiological pressures has shown that slit-like and crescentic lumens do not occur with uncomplicated atheromatous plaques. The residual lumen with plaques uncomplicated by acute thrombosis is usually eccentric in position but may be circular, ovoid, or D-shaped. Using a computer program we have shown there is a significant variation of arterial stenosis in different planes with ovoid or D-shaped lumens. The optimum shape which might be totally missed by examination in one radiological plane is not a cresent but an ovoid, the long axis of which is the same length as the normal vessel diameter. To prove this experimentally we have used glass tubes with artificially created stenoses in which the residual lumen is ovoid to stimulate diseased coronary arteries. *X* rays of these barium filled glass tubes through different degrees of rotation show that the percentage stenosis by diameter may vary by as much as 42 depending on the plane of view. Similarly underestimation may be seen if the incident *x* ray is not perpendicular to the object.

It is no longer necessary to suggest the occurrence of slit-like and crescentic lumens in order to explain underestimation of coronary stenosis in clinical coronary arteriography.

The crescentic lumen—fact or fiction?

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It is widely accepted that some significant stenoses can be seen only in one plane at coronary arteriography. The explanation of this phenomenon is usually taken to be the slit-like or crescentic shape of the coronary arterial lumen. Numerous illustrations of such luminal shapes are published but derive from arteries fixed for pathological examination in the collapsed state. Coronary arteries fixed after distention at physiological pressures give a far better approximation to the shape of the lumen in life. Hearts have been perfused fixed with formol saline at pressures of 100 and 150 mm Hg by tying a large cannula in the aorta. At such a pressure the aortic valve closes and the coronary arteries are perfused. The specimen is perfused for 24 hours after which fixation has produced enough rigidity for the vessels to remain in the fully distended state. The arteries are subsequently dissected en bloc free from the heart, decalcified, and examined by transverse cuts at 2 mm intervals. Normal arterial segments have a completely circular lumen. The internal elastic lamina is straight suggesting the artery is in the state analogous to complete dilatation. In diseased segments the majority of the lumens approximate to being circular although often placed eccentric to the mid-line of the vessel. Atheromatous plaques bulge outward at the expense of the media not inward to project into the lumen. Ovoid and D-shaped lumens are seen and are caused by flattening of the cap of hard fibrous plaques. Slit-like and crescentic lumens only occur with acute evolving lesions where a polypoidal mass of thrombus projects into the lumen.

Prevalence, diagnosis and prognosis of right ventricular necrosis in acute inferior myocardial infarction

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To compare the non-invasive methods of diagnosis of right ventricular necrosis, 51 consecutive patients with inferior myocardial infarction underwent serial radionuclide ventriculography, pyrophosphate (PYP) scintigraphy, cross sectional echocardiography, and 12 lead electrocardiography with the addition of unipolar right chest lead V4R. All 51 scintigrams confirmed inferior infarction, and additional uptake in the right ventricle was noted in 25. Significant correlation was observed between right ventricular ejection fraction (RVEF) determined by bolus and gated radionuclide techniques ($r=0{\cdot}92$) and although an echocardiographic estimate was achieved in 94% of patients all possible views were obtained in only 63% and agreement with the radioisotope methods was poor ($r=0{\cdot}45$). Clinical recognition of right ventricular infarction was noted in only three patients (mean RVEF 0·16) but severe right ventricular dysfunction (RVEF $<0{\cdot}25$) was seen in a further 22, and of these six suffered late hospital deaths. ST segment elevation $\geqslant 0{\cdot}5$ mm in V4R had a sensitivity of 92% in the recognition of severe right ventricular dysfunction but had a low specificity (40%). Those surviving hospital stay failed to show any improvement in resting RVEF two months later, six exhibiting persisting right ventricular dyskinesis and three developing features of predominant right ventricular failure.

Clinical recognition of right ventricular infarction was poor, use of the right chest lead V4R could lead to overdiagnosis, and echocardiography was limited by the complex geometry of the right ventricle. Three patients with poor right ventricular function had no evidence of right ventricular uptake by the PYP scintigram. We believe that functionally important right ventricular infarction is best detected by radionuclide ventriculography, particularly as profound right ventricular dysfunction appears to carry a high late hospital mortality.

Left ventricular thrombus in acute myocardial infarction: recognition by cross sectional echocardiography

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Anticoagulants have been advocated in acute myocardial infarction, when left ventricular thrombus is recognised by echocardiography. Of M mode and cross sectional echocardiographic studies in 95 consecutive patients with first transmural myocardial infarction and no anticoagulant therapy, 72 were suitable for serial evaluation of left ventricular thrombus. Echocardiography findings were related to patients' outcome. Thirty two patients had inferior myocardial infarction, and none had left ventricular thrombus. Peak creatine phosphokinase (CPK) values was 1633(1244) IU (mean (SD)). There was 1/32 deaths. Forty patients had anterior myocardial infarction. Sixteen of 40 (40%) had left ventricular thrombus on one or more echocardiographic studies (group 1). Twenty four patients with anterior myocardial infarction had no left ventricular thrombus (group 2). There was no difference in myocardial infarct size in group 1 compared with group 2 as judged by CPK values (2440(1411) *vs* 2271(1257) IU). In group 1, left ventricular thrombus appeared variously at three hours to 10 days postinfarction and in three patients spontaneously resolved. The presence of left ventricular thrombus was not unfavourably related to survival and functional class post myocardial infarction. There was 1/16 deaths and a mean class 1b (NYHA classification) in group 1 compared with 12/24 deaths ($p<0{\cdot}05$) and mean class 2b ($p<0{\cdot}01$) in group 2. Two deaths in group 2 were due to cardiac rupture. Systemic embolism occurred in one patient only who had inferior myocardial infarction and no left ventricular thrombus by echocardiography. Left ventricular thrombus is not predictable and is subject to spontaneous lysis. The presence of left ventricular thrombus detected by cross sectional echocardiography may not be associated with an unfavourable risk and, by splinting the infarcted segment, may even be beneficial following anterior myocardial infarction.

Reciprocal ST depression in acute myocardial infarction: relationship to coronary artery disease

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ST segment elevation in leads remote from those showing ST elevation during acute myocardial infarction (MI) has been attributed to benign electrical phenomena, distant myocardial ischaemia, or extensive myocardial damage. We studied 84 consecutive patients under 55 years with a first transmural MI. Treadmill exercise tests were performed at three and six weeks postinfarction. All had coronary angiography. Twenty eight (75%) of the 51 inferior and 19 (58%) of the 33 anterior infarcts had reciprocal ST depression of ≥ 1 mm during the acute phase. Fourteen (38%) of the 38 inferior infarcts with reciprocal depression and 3 (23%) of the 13 without reciprocal depression had significant left anterior descending (LAD) disease (NS). In inferior infarction reciprocal depression does not therefore predict LAD disease. Ten (26%) of the 38 inferior infarcts with reciprocal depression had ST depression in the same leads on exercise and five (50%) of these patients had significant LAD disease. Nine (32%) of the 28 patients who did not have ST depression in the same leads on exercise had significant LAD disease (NS). Seven (37%) of the 19 anterior infarcts with reciprocal depression and four (29%) of the 14 without reciprocal depression had significant right coronary artery (RCA) disease (NS). Reciprocal depression in anterior infarcts therefore does not predict significant RCA disease. Only one patient with anterior infarction had ST depression in the same leads on exercise and there was no significant RCA disease.

In conclusion, neither reciprocal ST depression during acute myocardial infarction nor exercise induced ST depression in the same leads early post infarction predict significant coronary artery disease in the reciprocal territory.

Digital subtraction angiography: a screening procedure for patency of coronary artery bypass grafts

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A prospective study was undertaken to evaluate venous digital subtraction angiography (DSA) in the detection of coronary graft presence and patency. Patients with recurrence of chest pain following coronary grafting were studied by venous DSA and conventional angiography. Forty millilitres of iohexol were injected into the right atrium via a 5F catheter at 25 ml per second per run. Images were acquired in both left anterior oblique 45° and right anterior oblique 5° projections. Graft patency and presence was assessed by three independent observers without prior knowledge of which grafts had been inserted. Sixteen patients with 37 grafts were studied. Twenty six grafts were patent. There was agreement in 11 patients, seven being correctly assessed. There was partial agreement in the remaining five patients. All occluded grafts were correctly identified; 17, 18, and 19 of the 26 patent grafts were identified by the three observers respectively. The graft to the left anterior descending artery was least well demonstrated, with five out of 12 patent grafts missed. Patent grafts to the left circumflex and posterior descending arteries were not identified in one out of six and two out of eight cases respectively.

These figures yield a specificity of 100% (no false positives) and a sensitivity of 78%. A graft identified by DSA is definitely present but patient grafts may be missed.

Free radicals and ischaemic injury: allopurinol improves myocardial protection during global ischaemia

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Ischaemia-induced breakdown of adenine nucleotides provides increased substrate for xanthine oxidase (the enzyme responsible for uric acid production from hypoxanthine and xanthine). Subsequent aerobic reperfusion increases oxygen availability so that xanthine oxidase activity and the consequent production of the superoxide free radical increases dramatically. During ischaemia and particularly during reperfusion, superoxide free radicals might play a role in cellular injury. We have investigated whether pretreatment with the specific xanthine oxidase inhibitor, allopurinol, can enhance myocardial resistance to ischaemia and reperfusion injury during normothermic (37°C) and hypothermic (21°C) arrest with St Thomas' Hospital cardioplegic solution. Rats were pretreated with allopurinol (20 mg/kg orally for two days and intravenously on day 3 prior to excision of the heart). Using an isolated "working" rat heart preparation, hearts were perfused aerobically for 20 minutes followed by three minutes of cardioplegic infusion and either 27 minutes of 37°C global ischaemia or 300 minutes of 21°C global ischaemia (with three minute reinfusions of cardioplegia every 30 minutes) and reperfusion for 15 minutes. Postischaemic recovery (expressed as a percentage of preischaemic control) of aortic flow, cardiac output, stroke volume, and stroke work in the 37°C control group (n=8) were 22·1(4·5)%, 36·9(7·5)%, 40·9(9·7)%, and 36·4(11·0)% respectively, whereas these values in the allopurinol pretreated group (n=8) were 54·8(16·3)%, 61·6(15·1)%, 59·2(16·1)% and 51·8(17·2)%. Postischaemic recovery values for these indices in the 21°C control group (n=6) were 21·0(11·0)%, 29·2(9·4)%, 30·8(9·3)%, and 24·8(9·1)% and in the allopurinol pretreatment group (n=6) they were 24·8(8·1)%, 32·2(8·5)%, 37·2(8·1)%, and 31·2(8·5)%. Thus although allopurinol pretreatment significantly improved myocardial resistance to ischaemic injury at normothermia, there was no effect with hypothermia. The most likely explanation of these results is that both allopurinol and hypothermia act to inhibit superoxide free radical production but hypothermia masks any allopurinol effect.

Limitation of infarct size: a comparative study with six drugs

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Using a closed chest dog, three calcium antagonists verapamil, nifedipine, and diltiazem, two beta blocking agents metoprolol and cetamolol, an anti-inflammatory agent flurbiprofen, and a xanthine oxidase inhibitor allopurinol were evaluated for their ability to limit myocardial infarct size following either 24 or 48 hour periods of coronary artery embolisation. Coronary arteries were embolised by injecting 2·5 mm beads into the coronary network via a carotid artery cannula. Cerium-141 labelled microspheres were given immediately thereafter to mark the blood flow pattern around the ischaemic area. Continuous infusion of the drug for 24 or 48 hours (saline given to controls) was then initiated. At the end of the ischaemic time period the hearts were removed, sliced, and the infarct area visualised using tetrazolium staining techniques. The risk zone was visualised following autoradiography of the slices. The results of these studies clearly show that both the beta blockers, metoprolol and cetamolol, as well as the non-steroidal anti-inflammatory agent flurbiprofen, had no effect in limiting infarct size; whereas the three calcium antagonists verapamil (44% limitation at 24 hours), nifedipine (40% limitation at 24 hours and 25% limitation at 48 hours), and diltiazem (30% limitation at 48 hours) and the xanthine oxidase inhibitor allopurinol (42% limitation at 24 hours), showed a significant (p<0·001) effect on limiting the extent of tissue necrosis.

Thus it can be seen that only certain classes of pharmacological agents appear to limit myocardial infarct size in this experimental preparation. The mechanism of action of these that appear beneficial is at present being studied.

Untreated chronic heart failure: effects at rest and on exercise of introducing diuretic therapy

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The physiological effects of introducing diuretic therapy in patients with untreated chronic heart failure are poorly documented. We observed clinical and neuroendocrine variables, at rest and on upright exercise, before and after the introduction of frusemide in 10 patients with chronic heart failure who had been symptomatic for at least one month but who had not had any prior therapy. Five patients had dilated cardiomyopathy, four chronic ischaemic heart disease, and one rheumatic mitral valve disease. Before diuretics, the patients were breathless on mild exertion, had radiological cardiomegaly and pulmonary venous hypertension, and raised venous pressure or a fourth heart sound; one had peripheral oedema. Treadmill exercise time was 10·8 (2·5) (mean (SEM)) minutes, using a slow protocol. Plasma renin activity and aldosterone were normal in all patients, at rest and on exercise. Plasma noradrenaline was elevated at rest and increased further on exercise. (p<0·05). After one month of frusemide, patients were less breathless, had lost 3·6 (1) kg (p<0·05), and doubled their exercise time. Plasma renin activity and aldosterone were now abnormally elevated at rest, and more so on exercise; plasma noradrenaline was normal at rest but remained elevated on exercise.

Although diuretics cause short term clinical improvement in heart failure, reducing resting sympathetic activity, they achieve this at the expense of activation of the renin-angiotensin system, which may have important long term implications for therapy and progression of the disease.

Intravenous captopril for severe heart failure

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We studied the effect of intravenous administration of captopril in 26 patients with chronic heart failure. Plasma free captopril was measured by radioimmunoassay. A bolus dose of 25 mg (14 patients) produced a very rapid reduction in systemic vascular resistance (−31%) with maximal change at 5 min after injection. Cardiac output rose 20% and mean systemic pressure fell 18%. Pulmonary end diastolic and right atrial pressures fell more slowly with a nadir at 60 min. The effect on systemic vascular resistance decreased over 90 min, when a 9% reduction persisted. There was an initial fast distribution phase of plasma free captopril while the elimination half life between 1·5 and 8 h after the dose was 3·36(SE 0·25) h. A series of seven incremental doses (0·3125 mg to 20 mg total) was given to 12 patients. Progressive changes in systemic vascular resistance, cardiac output, and systemic pressure were seen between 0·3125–5 mg with no further change thereafter. Plasma free captopril at the onset of the plateau of the dose-response curve was 150 ng/ml: this is considerably higher than predose concentrations found during chronic therapy with 25–50 mg thrice daily and suggests that larger doses or more frequent administration might be needed for a sustained maximal effect.

Intravenous captopril will be useful for intensive care patients with cardiac failure.

Renal vascular response to neuroendocrine vasodilatation in chronic heart failure

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Activation of the renin-angiotensin and sympathetic systems in chronic heart failure causes important renal vasoconstriction. The renal vascular response to vasodilatation by inhibition of these neuroendocrine systems was assessed in 15 patients with stable heart failure on diuretics: measuring renal plasma flow (with ^{123}I-OIH) and cardiac haemodynamics, to derive renal blood flow (RBF), renal vascular resistance, and the percentage cardiac output to the kidneys (%CO), before and after one month each of captopril and prazosin, in a double blind crossover study. Captopril reduced systemic ($p<0{\cdot}05$) and renal ($p<0{\cdot}01$) vascular resistance, increasing RBF ($p<0{\cdot}05$) and %CO ($p<0{\cdot}05$). The increase in RBF correlated with control plasma renin activity ($r=0{\cdot}53$, $p<0{\cdot}05$). Although prazosin also reduced systemic vascular resistance ($p<0{\cdot}05$), renal vascular resistance increased ($p<0{\cdot}01$), and RBF and %CO fell ($p<0{\cdot}05$). Weight fell 1·7 kg ($p<0{\cdot}05$) on captopril but increased 3·0 kg ($p<0{\cdot}05$) on prazosin; these changes correlated inversely with RBF changes ($r=-0{\cdot}53$, $p<0{\cdot}01$).

Sympathetic inhibition with prazosin causes systemic vasodilatation, which diverts blood from the kidney and may result in fluid retention. Inhibition of the renin-angiotensin system with captopril causes preferential renal vasodilatation and allows renal perfusion to improve.

Neuroendocrine and haemodynamic interactions during exercise in chronic heart failure: double blind comparison of captopril and prazosin

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We report the first double blind study of clinical, neuroendocrine, and haemodynamic interactions in moderate chronic heart failure, at rest and during upright exercise, comparing inhibition of the renin-angiotensin-aldosterone (RAA) system (captopril) and of the alpha$_1$ adrenergic sympathetic system (prazosin). Sixteen patients on diuretics were studied; each drug was crossed over at one month. Control plasma renin activity (PRA), aldosterone (Aldo), and noradrenaline (NA) were elevated at rest and increased on exercise ($p<0{\cdot}05$). Control left ventricular filling pressure (LVFP) was elevated, correlating with PRA and Aldo ($r>0{\cdot}51$, $p<0{\cdot}05$). Systemic vascular resistance (SVR) was elevated, and vasodilatation during exercise was limited by PRA and NA release ($r=0{\cdot}82$, $p<0{\cdot}01$; $r=0{\cdot}62$, $p<0{\cdot}05$). On captopril there were reductions in Aldo ($p<0{\cdot}05$) and LVFP ($p<0{\cdot}05$), at rest and on exercise, and dyspnoea was relieved. SVR was lower at rest ($p<0{\cdot}05$) and on exercise ($p<0{\cdot}05$); vasodilatation on exercise was no longer impaired by

RAA activation, and exercise capacity increased by 35% ($p<0.01$). On prazosin, NA and Aldo increased initially ($p<0.05$), fluid retention increased weight ($p<0.05$), LVFP was unchanged, and dyspnoea was not relieved. Resting SVR was reduced ($p<0.05$), but exercise vasodilatation remained limited by RAA and sympathetic activation, and exercise capacity did not improve.

These results illustrate the importance of the renin-angiotensin-aldosterone system in chronic heart failure, at rest and also on exercise.

Right ventricular dysfunction dictates the therapeutic response in chronic cardiac failure?

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In patients with chronic cardiac failure, vasodilator therapy produces a variable therapeutic effect. The purpose of this study was to determine whether the response to afterload reduction is affected by associated right ventricular dysfunction in patients with chronic left ventricular failure. Fifteen male patients with New York Heart Association grade III–IV chronic cardiac failure secondary to coronary heart disease were studied. Heart rate was obtained from the electrocardiogram, blood pressure by cuff sphygmomanometer, cardiac output by thermodilution, and ejection fraction of right and left ventricle from gated technetium ventriculography. In 10 patients with preserved right ventricular function (RVEF >25%), LVEF ranged from 10 to 29%. Left ventricular ejection fraction ranged from 10 to 23% in five patients with right ventricular dysfunction (RVEF 12–24%). Exercise tolerance was similar in both groups (mean exercise time 178(21) s and 146(16) s. In both groups afterload reduction with felodipine produced a modest increase in heart rate from 71(5) beats/min to 79(5) beats/min and 79(6) beats/min to 85(7) beats/min secondary to fall in mean blood pressure from 101(4) mm Hg to 87(4) mm Hg ($p<0.05$) and 83(5) to 78(5) mm Hg. In patients with preserved right ventricular function cardiac index increased from 2·5 to 3·8 l/min/m^2 ($p<0.01$) but in patients with right ventricular dysfunction cardiac index increased insignificantly from 2·3(0·4) to 2·6(0·4) l/min/m^2. In conclusion, in patients with ischaemic chronic cardiac failure with a similar degree of left ventricular dysfunction, associated right ventricular abnormality predicts patients with a limited therapeutic response to afterload reduction.

Increased sensitivity of the denervated human heart to isoprenaline before and after beta blockade

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Denervation may increase target organ sensitivity to its chemical transmitter. We tested this hypothesis by studying the heart rate (HR) response to isoprenaline of the denervated donor heart (DH) as compared to the innervated recipient heart (RH) in eight patients who underwent heterotopic cardiac transplantation because of congestive cardiomyopathy (2) or ischaemic heart disease (6) six to 12 months earlier. All patients were well compensated and did not require treatment for heart failure. The resting heart rate was higher in the donor heart (101·4(3·7) beats/min compared to the recipient heart (90·5(6·5) beats/min; $p<0.04$). Incremental intravenous infusion of isoprenaline (5 ng, 10 ng, and 15 ng/kg/min) raised heart rate to a greater extent in the donor heart at the two higher doses (21·9(3·5) and 32·4(4·7) beats/min for donor heart *vs* 14·8(2·7) and 22·8(4·2) beats/min for recipient heart; $p<0.01$ and $p<0.003$ respectively). Following 0·1 mg/kg of intravenous propranolol, the resting heart rate decreased similarly in the donor heart (−12(2) beats/min $p<0.01$) and the recipient heart (−14(2·5) beats/min; $p<0.01$). There was little heart rate increase in both hearts at 5 ng and 10 ng/kg/min, but at higher doses the donor heart was still more responsive (15 ng/kg/min: 11·2(2·1) beats/min for donor heart *vs* 6·5(1·9) beats/min for recipient heart; $p<0.01$; 20 ng/kg/min: 14·1(2·8) beats/min for donor heart *vs* 6·7(1·6) beats/min for recipient heart; $p<0.005$; 25 ng/kg/min: 17·7(3) beats/min for donor heart *vs* 8·1(1·6) beats/min for recipient heart; $p<0.002$).

In patients with cardiac transplantation, the denervated heart is more sensitive to the chronotropic effect of isoprenaline. This may reflect increased density or affinity of the beta receptors in the denervated heart.

Beta blockade produces greater attenuation of exercise tachycardia in the denervated human heart

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Heterotopic cardiac transplantation offers an opportunity to assess the effect of pharmacological agents on the innervated recipient and the denervated donor heart simultaneously in the same patient. The effect of acute beta blockade on the heart rate (HR) response to exercise was studied in six patients 6–12 months after heterotopic cardiac transplantation, using a modified Bruce protocol before and after the administration of intravenous propranolol (0·1 mg/kg). The resting heart rate decreased similarly and significantly ($p<0·05$) in both the donor (DHR 15·5(2)) and recipient heart (14·3(2·6)). Before beta blockade the heart rate response at peak exercise was similar for both the donor (DHR 38(3·5)) and recipient heart (RHR 48(3)). After beta blockade the peak exercise response for the donor heart was 20·9(3) compared to 38·3(3·5) for the recipient heart which represents a two fold greater attenuation in the donor heart. In contrast, the increase in heart rate of both donor and recipient hearts in early exercise (first three minutes of the Bruce protocol) as well as the decrease during the first three minutes post exercise was unaffected by beta blockade.

It is concluded that the heart rate response of the denervated heart, at peak exercise, is markedly blunted by beta blockade and that greater caution is required in using these drugs in transplanted patients.

Adverse effect of high dose aspirin on prostacyclin generation by autogenous vein grafts

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External jugular vein grafting into the ipsilateral carotid artery in the rabbit was used as a model to study the effect of different doses of aspirin (ASA) given in combination with dipyridamole (DIP), or DIP alone on vein graft prostacyclin (PGI_2) production. Animal groups consisted of: A, no treatment ($n=6$): B, low dose ASA (0·5 mg/kg/24 h) plus DIP ($n=6$): C, high dose ASA (40 mg/kg/24 h) plus DIP ($n=6$): D, DIP alone ($n=6$). DIP (8 mg/kg/24 h in divided doses) was started 48 h prior to operation and ASA on the first postoperative day. Both drugs were given for one month. Vein grafts (VG) and non-grafted artery (A) and vein (V) were then removed, opened and placed in a template with the luminal surface forming the base of a well. Radioimmunoassay was used to measure PGI_2 levels in 500 μl aliquots of HEPES buffer placed in the well. Results from group A showed that grafting of a vein into the arterial system results in PGI_2 levels which almost reached arterial levels (mean for $V=122$ pg (range 104–144), $VG=309$ pg (range 223–428), $A=389$ pg (range 299–507). Vein grafts and non-grafted vessels of group C animals produced significantly less PGI_2 than corresponding vessels of the other three groups ($p<0·01$ for all comparisons). In group B animals there was a reduction in VG PGI_2 as compared to group A animals, but the difference did not reach statistical significance.

High dose ASA therefore reduces prostacyclin in vein grafts, explaining the previous finding of enhanced platelet deposition in these animals. This in turn will cause the increase in graft intimal thickness also previously demonstrated. Because aspirin may have an adverse effect on long term graft survival through promotion of intimal hyperplasia, warfarin may be a better agent for the prevention of thrombotic occlusion in the early postoperative period.

Preparation of human saphenous vein for coronary surgery impairs prostacyclin production

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Immediate postoperative platelet deposition is thought to contribute both to early and to late coronary vein graft occlusion. We investigated whether routine preparation of saphenous vein leads to impaired prostacyclin production which would favour platelet deposition. Treatment—for example, with prostacyclin—might then offer scope for its prevention. Saphenous vein was harvested (*a*) immediately after removal or (*b*) after routine preparation by adventitial stripping, side branch ligation, 1 min distension at <300 mm Hg, and storage for up to 2 h in 0·9 g/l NaCl at 23°C. Weighed segments of vein were incubated for three 10 min periods in fresh 1 ml aliquots of Tris buffer (0·14 mol NaCl, 15 mmol Tris/HCL, pH 7·4); each segment was then cut into three weighed pieces which were incubated for 3 min in 0·3 ml Tris buffer with vortex mixing for the first 15 s. At the end of each incubation, the vein was removed, indomethacin (3·3 μ/ml) was added, and the 6-ketoprostaglandin F_1 concentration in the buffer was measured by radioimmunoassay. Unstimulated prostacyclin production was constant over the first three periods and averaged 1·7(0·5) pg/ml/min in control vein and 1·9(0·5) pg/ml/min in prepared vein (NS, $n=5$). Prostacyclin production rose with vortex stimulation 11(2) fold in control vein but only 4(1) fold in prepared vein ($p<0·05$). In a larger series ($n=13$), vortex stimulated prostacyclin production proceeded at 16(2) pg/mg/min in control vein and 7(1) pg/mg/min in prepared vein ($p<0\cdot05$). Morphological examination showed similar endothelial preservation in the segments from control and prepared vein. The data indicate that the capacity of vein to produce prostacyclin becomes impaired during surgical preparation.

Metabolic damage to human saphenous vein during preparation for coronary bypass surgery

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Coronary graft patency may be affected by the procedures used for intraoperative preparation of vein. Tissue damage caused during routine preparation and its component steps was quantified by measuring ATP and its metabolites by HPLC. Vein was frozen in liquid N_2 after dissection (control); after storage in blood at 23°C for up to 2 h (stored); after side branch ligation and adventitial stripping (manipulated); after manipulation followed by 1 min distension at <300 mm Hg (limited pressure) or with gentle unlimited pressure; or from vein unused after completion of the last proximal anastomosis (prepared vein). The ATP content of control vein, 480(30) nmol/g ($n=28$), was reduced to 260(40) nmol/g ($n=15$, $p<0\cdot001$) in prepared vein using distension at <300 mm Hg; the ATP:ADP ratio was reduced from 2·4(0·1) to 1·3(0·1) ($p<0\cdot001$). The ATP content in vein prepared using unlimited pressure distension was 170(20) nmol/g ($n=23$) and the ATP:ADP ratio was 0·9(0·1) ($p<0\cdot05$ *vs* distension at <300 mm Hg). Inosine and hypoxanthine concentrations were elevated in prepared vein relative to control ($p<0\cdot05$). Storage caused a slow fall in ATP concentration to 350(40) nmol/g control ($n=6$, $p<0\cdot05$) but did not change ATP:ADP ratio. Manipulation alone caused no change in ATP content or ATP:ADP ratio, but manipulation followed by limited pressure distension reduced ATP:ADP ratio to 2·1(0·1) ($n=8$, $p<0\cdot05$ *vs* control), and manipulation followed by unlimited pressure distension reduced ATP content to 250(20) nmol/g and ATP:ADP ratio to 1·2(0·1) ($n=8$), $p<0\cdot001$). The data provide clear evidence of metabolic damage to vein during surgical preparation. The single step of unlimited pressure distension led to the same changes seen in prepared vein whereas storage was relatively innocuous.

Screening for carotid disease in patients with coronary artery disease

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The prevalence of carotid disease has been variably reported as being present in up to 18% of patients with coronary artery disease (CAD) undergoing coronary artery bypass surgery. We have looked prospectively for evidence of carotid disease in 100 consecutive patients with symptomatic CAD undergoing coronary angiography and 100 controls having minor operations, using continuous wave (CW) Doppler imaging and Duplex scanning. CW Doppler imaging and Duplex scanning are accurate techniques in the direct non-invasive assessment of carotid disease. We have carried out a blind prospective comparison with biplanar angiography, in which the sensitivity and specificity of CW Doppler imaging was 90% and 98% respectively in the detection of $\geq 50\%$ internal carotid stenosis ($n=96$), and that of Duplex scanning was 93% and 98% respectively ($n=85$). Ten per cent of CAD patients were found to have significant disease ($\geq 50\%$ stenosis or occlusion) affecting the internal carotid artery or carotid bifurcation compared with 3% of controls ($p<0\cdot05$). Seven CAD patients had no cerebral symptoms and five had no carotid bruit. Of nine affected patients who have had coronary angiography so far, four have undergone carotid endarterectomy prior to coronary artery bypass surgery without complication. A further two patients have been referred for carotid surgery.

Measurement of infarct size by thallium-201 rotating slant-hole tomography: a human pathological correlation

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Thallium-201 scintigraphy was performed in 18 patients with a first myocardial infarct before death. All had rotating slant-hole tomography, 17 had anterior, 45° left anterior oblique, and left lateral planar scans also. Post mortem examination was performed within four hours of death, hearts frozen, then sliced and incubated in nitroblue tetrazolium. Stereological analysis of heart slices to give percentage volume defect was compared with results from quantifying planar scans and 12 reconstructed tomographic slices. Three sets of tomograms and two planar series could not be assessed: movement artefact affected all scans in one patient; extensive apical defects in tomograms could not be quantified in two patients; unsuspected old infarction confused planar measurement in one patient, "cross talk" was observed in the tomograms. Blur artefacts were not a problem in this series but have been observed to hinder identification of smaller defects. Tomography improved the correlation of thallium defect size with pathology ($r=0·81$) over planar scans ($r=0·65$). Two patients had notably larger tomographic and planar thallium defects than pathological infarct size, presumably due to peri-infarctive ischaemia. If these were excluded, tomographic infarct size correlated with pathological infarct size ($r=0·97$), and for a subset of 11 patients with all data, tomography improved the correlation of thallium infarct size from $r=0·88$ to $r=0·95$.

Thus thallium-201 rotating slant-hole tomography may be a useful research tool for sizing moderate first time infarcts in intervention studies, when satisfactory reconstruction can be achieved.

Clinical role of thallium-201 scintigraphy in the management and prognosis of coronary artery disease

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The clinical impact of thallium-201 (Tl-201) scintigraphy in coronary artery disease was reviewed in 128 consecutive patients who were referred for routine investigation and followed for a mean of 13(1) months. Exercise and redistribution image data were collected in multiple projections and interpreted by combined visual and semiquantitative means. A segmental image defect was accepted as indicating the presence of coronary artery disease. Normal Tl-201 images were obtained in 69 of 79 (87%) diagnostic studies. Sixty four (82%) were spared diagnostic coronary arteriography; five proceeded to coronary arteriography for persisting symptoms (two had normal arteriograms, two had minor (<70% stenosis) single vessel disease, one had double vessel disease). Conversely, coronary arteriography was normal in two of 10 (20%) patients with unequivocal image defects. Tl-201 scintigraphy was performed as a functional complement to coronary arteriography in 49 patients, influencing the decision for surgery in 33 and determining the presence or absence of myocardial ischaemia in 16 patients with equivocal coronary arteriograms. Myocardial ischaemia was confirmed in eight of these 16 patients and normal data were obtained in eight patients. During the follow up period of 13(1) months none of the 77 patients with normal Tl-201 scintigrams died, sustained myocardial infarction, or other major cardiac event.

These data confirm both the vital role of Tl-201 scintigraphy in the management of patients with suspected or proven coronary artery disease and the excellent prognostic value of a normal Tl-201 scintigram.

A new technique for displaying tomographic images of perfused myocardium obtained using Tl-201 and their relationship to the coronary arteries

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Conventional transverse tomograms with thallium-201 represent oblique slices through perfused myocardium which do not correspond to the major axes of the left ventricle. It is difficult to relate observed defects easily to coronary anatomy. We have developed a new technique for the presentation of myocardial tomograms which allows the observer to perceive the shape of the Tl-201 distribution directly. The surface of the myocardium is found by applying an interactive thresholding technique to a set of conventional transverse slices. Computer graphics techniques are used to display a "shaded image" of that surface on a TV screen, showing the three dimensional shape of the myocardial surface from any chosen aspect.

As a further aid to image interpretation we have digitised a set of normal preserved coronary arteries. Using scaling and transformation techniques these arteries are "mapped" on to the myocardial tomograms, and a shaded surface image produced with superimposed coronary arteries. This provides a familiar anatomical framework for locating perfusion defects and may be of value in the identification of diseased vessels.

Improved detection of coronary heart disease by gated thallium scanning

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Thallium 201 imaging is established for the assessment of myocardial perfusion. This study evaluates the use of gating the thallium image to the ECG to assess both right and left ventricular function and perfusion. Gated thallium scans were obtained from 100 consecutive male patients undergoing coronary angiography. Eighty megabecquerels of thallium 201 were injected intravenously during the last 30 seconds of maximal exercise and scans obtained in the anterior, 40° and 70° left anterior oblique projections, each for 5 min using a gammacamera. Analysis was performed by three independent observers, normal values being obtained from 12 healthy volunteers. Regional wall motion was assessed visually from the gated image and interobserver variation was small (0·9% for 1280 segments). Coronary angiography was performed within 48 hours of scanning, with a 50% reduction in luminal diameter being considered significant. Segmental perfusion defects were detected in 89% of patients with significant coronary disease, 75% with defects subtended by arteries with 50%–75% stenosis, and 94% with 99–100% stenosis. The addition of regional wall motion abnormalities identified 95% of patients with coronary disease. Fifty seven patients were noted to have inferior left ventricular defects, and right ventricular perfusion defects were seen in 20 of these scans. Seventy seven per cent of these patients had $>90\%$ obstruction of the right coronary artery.

In conclusion, coronary artery lesions greater than 50% produce exercise perfusion defects and wall motion abnormalities of both the right and left ventricle, which are reliably detected by gated thallium scanning.

T lymphocyte subsets and function in dilated cardiomyopathy in East Africa

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It has been suggested that an excessive or inappropriate immune reaction may be partly responsible for the myocardial damage which leads to dilated cardiomyopathy. In order to determine if there is such a reaction in patients with dilated cardiomyopathy (DC) in East Africa we have measured the percentage of T lymphocyte subsets using monoclonal antibodies (Ortho) to identify the total percentage of T lymphocytes (OKT3 positive), helper-inducer T cells (OKT4 positive), and suppressor-cytotoxic T cells (OKT8 positive) in 20 patients (nine men; mean age 32·8(13) years) with DC and 20 age and sex matched normal controls. The results showed that the total percentage of T cells were similar in both groups (patients: 65·6(2·6)%; controls: 64·1(2·0)%) while the percentage of helper-inducer cells was significantly higher in the DC group (patients: 44·7(1·8)%; controls: 32·8(2·0)%; $p<0·001$) and the percentage of suppressor cells was slightly lower (patients: 28·4(2·2)%; controls: 33·6(1·6)%). The helper:suppressor cell ratio was higher than the normal range in eight of the 20 patients. Seven of the eight patients with these high ratios were studied within three months of onset of their symptoms. Repeat measurements were done in seven patients, and in one patient there was a fall in the helper:suppressor ratio over five months. Lymphocyte functional assays (mixed lymphocyte reaction) were done in six patients and six controls, and in three patients the "stimulation index" was above the control group range. These results indicate that an excessive immune reaction may be part of the pathogenesis of dilated cardiomyopathy in Africa.

Cardiac hypertrophy, hypertrophic cardiomyopathy and hyperparathyroidism—an association

Farieda Fortune, R A Greenbaum, P Dandona, C Symons
The Royal Free Hospital, London

Patients with primary hyperparathyroidism were investigated to detect and categorise cardiac hypertrophy. In a separate group with hypertrophic cardiomyopathy, estimation of parathyroid hormone level was made. A third group with hypercalcaemia alone was studied. All had M mode echocardiography. Estimation of septal and left ventricular wall thickness was made at mitral valve closure, and minimum cavity dimension was estimated. The presence of systolic anterior motion of the mitral valve and mid-systolic closure of the aortic valve were noted. Echocardiographic estimations were made without the knowledge of the patient's biochemical status. Echocardiograms were classified as normal, symmetric left ventricular hypertrophy, asymmetric septal hypertrophy, and hypertrophic cardiomyopathy.

Parathyroid hormone was measured by radioimmunoassay using an antibody technique directed against the mid-molecular peptide of the hormone. Forty one patients were studied: namely, (*a*) primary hyperparathyroidism (16 cases): five (31%) had symmetric left ventricular hypertrophy, five had hypertrophic cardiomyopathy, four had asymmetric septal hypertrophy, and two had no ventricular hypertrophy. All were hypercalcaemic. (*b*) Hypertrophic cardiomyopathy (18 cases): five (28%) were found to have high levels of circulating parathyroid hormone. None had hypercalcaemia. (*c*) Hypercalcaemia without hyperparathyroidism (seven cases): none had any cardiac hypertrophy.

It is concluded that (*a*) excess circulating parathyroid hormone is frequently associated with cardiac hypertrophy, including hypertrophic cardiomyopathy and (*b*) hypercalcaemia of itself does not give rise to cardiac hypertrophy.

Persistent echocardiographic and endomyocardial biopsy abnormalities after Coxsackie B myopericarditis

D O'Neill, G Lindop, H J Dargie
Departments of Cardiology and Pathology, Western Infirmary, Glasgow

In order to assess the long term effects on cardiac function of Coxsackie B myopericarditis (CM) we performed M mode echocardiography on 47 consecutive patients (24 male and 23 female, aged 42(13) years at a mean follow up time of 40 months (range 6–70 months) after diagnosis. These patients were compared with 42 normal control subjects (20 male and 22 female, aged 32(12) years. Mean right ventricular dimension was significantly greater at 2·35 cm in the CM group compared with 1·95 cm in the control group ($p<0\cdot001$); increased right ventricular dimension (>2·6 cm) was present in 11 patients, and in seven this was the only abnormality found. Mean left ventricular internal dimensions were similar in both groups but in three patients left ventricular end diastolic dimensions were similar in both groups but in three patients left ventricular end diastolic dimension was increased (>5·7 cm), and seven patients showed a reduction in left ventricular shortening fraction to <25%. In all, echocardiographic abnormalities were found in 16 patients (34%), of whom 13 were male. Nine patients, eight of whom had an abnormal echocardiogram, also underwent endomyocardial biopsy. Three biopsies showed continuing active myocarditis with ongoing myocyte destruction, and six showed focal inflammation with replacement fibrosis indicating healing myocarditis. We conclude that persisting echocardiographic abnormalities are common after CM, right ventricular enlargement being the most frequent finding which may occur in the absence of detectable left ventricular abnormality. Persistent low grade myocarditis may occur even in the absence of symptoms or cardiac enlargement. No progression to dilated cardiomyopathy has been observed so far.

Right ventricular wall thickness in hypertrophic cardiomyopathy: the relationship to clinical and prognostic features

R Foale, A Kleinebenne, P Nihoyannopoulos,
W J McKenna
Hammersmith Hospital, Royal Postgraduate Medical School, London

Right ventricular hypertrophy (RVH) is found at autopsy in the majority of patients with hypertrophic cardiomyopathy (HCM) who die suddenly. Until recently it has been difficult to measure right ventricular wall thickness in vivo. We have performed dual M mode and cross sectional echocardiography using right ventricular specific views to assess the presence of RVH and its relationship to prognostic features in 83 consecutive adults with HCM. Twenty four normal subjects were studied for comparison. Anterior, posterior, and diaphragmatic right ventricular wall thickness was evaluated from 13 right ventricular segments; 73 (88%) of patients with HCM and 20 (83%) normal subjects had recordings from which at least eight segments could be measured. In patients with HCM, right ventricular wall thickness ranged from 3–20 mm compared to the normal group in which right ventricular wall thickness measured 4 mm. Thirty two (44%) patients with HCM had at least one segment >5 mm and were thus considered to have RVH. In this group, the coefficient of variation of right ventricular wall thickness was 0–30% (median 9). In HCM patients without RVH, the coefficient of variation was 0–15% (median 11), which was similar to normals, 0–15% (median 10). RVH in patients with HCM was symmetric in all but three and was more common in those with severe left ventricular hypertrophy (LVH of 20 mm ($p<0\cdot02$). RVH was neither related nor associated with a raised LVEDP, pulmonary arteriolar resistance, and RV or LV gradients. RVH was associated with dyspnoea ($p<0\cdot05$) and with ventricular tachycardia during 48 hour Holter ECG ($p<0\cdot01$). RVH is common in HCM, appears to be due to primary myopathic involvement rather than changes secondary to LV dysfunction, and is associated with ventricular tachycardia. RVH may improve the specificity of ventricular tachycardia as a marker for sudden death in adults with HCM.

Prognostic indicators in dilated cardiomyopathy

R Diaz, A Obasohan, H Newman, J F Goodwin, Celia Oakley
Hammersmith Hospital, Royal Postgraduate Medical School, London

One hundred and sixty nine patients aged 18 to 64 years with dilated cardiomyopathy were studied. Known causes of left ventricular failure were excluded by definition. All patients underwent cardiac catheterisation and none had coronary artery disease. At the time of diagnosis the left ventricular end diastolic pressure was elevated (24(10) mm Hg); the ejection fraction was depressed (29(13)%); and both the left ventricular end systolic volume (105(57) ml/m^2) and the left ventricular end diastolic volume (148(64) ml/m^2) were increased. The mean follow up was 5·5(4·2) years. During this period 102 (60%) patients died. The average duration from the onset of symptoms to death was 4·1 (3·7) years. One year and five year mortality rates were 34·7% and 59·4% respectively with most deaths (44·1%) occurring during the first two years of follow up. When the characteristics of the survivors and non-survivors were compared non-survivors had higher left ventricular end diastolic pressure (23 compared with 17 mm Hg; $p<0·001$); lower ejection fraction (25 compared with 33%; $p<0·005$); and larger left ventricular end systolic volume (129 compared with 87 ml/m^2; $p<0·01$) and left ventricular end diastolic volume (173 compared with 131 ml/m^2; $p<0·01$) than did the survivors. Recent pregnancy and heavy alcohol intake did not seem to influence prognosis. Ventricular tachycardia or multiforms on Holter recording were more common in the non-survivors but were a feature of worse left ventricles and not an independent risk factor. When treatment was compared no differences were found between the two groups and vasodilators could not be shown to influence survival, having been given to about a quarter of the patients in each group. Dilated cardiomyopathy has a high mortality with survival time apparently related only to the severity of left ventricular impairment at presentation.

Radiation hazards associated with percutaneous transluminal coronary angioplasty

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Christie Hospital and Holt Radium Institute and Manchester Royal Infirmary, Manchester

Percutaneous transluminal coronary angioplasty is a recognised technique in the management of coronary disease. The Simpson method as been adopted in this unit. The radiation dosage to patients and operators was studied. Scattered dose measurements were made at the thyroid, ovaries, and testes in 15 patients. Whole body integral doses to patients were determined from exposure area products. Doses to patients decreased with experience and new guide wire systems. Data concerning staff indicated the operator would exceed the occupational dose limit to the eye if more than 120 percutaneous transluminal coronary angioplasties were performed per year. When other invasive procedures including catheterisation and pacing were included this limit dropped to only 60 examinations per year. Likewise repeat cardiac catheterisation increases gonadal doses to patients.

The following recommendations are made (*a*) operators should consider extra eye protection such as lead glass spectacles, photochromic lenses, or portable acrylic screens and (*b*) patients undergoing percutaneous transluminal coronary angioplasty during the reproductive period should have gonadal protection at the time of angioplasty and during subsequent procedures. It is emphasised that the operator is at major risk of cataract development if such precautions are not taken.

Pericardoscopy—a new approach in the management of pericardial effusions of unknown aetiology

S Westaby
Royal Postgraduate Medical School, Hammersmith Hospital, London

Treatment of reaccumulating pericardial effusions with cardiac tamponade often presents difficulties. Failure to obtain a diagnosis by needle aspiration and cytology is usually followed by subxiphoid surgical drainage, though access to anything but the diaphragmatic pericardium is limited. Pericardoscopy was used to inspect the interior of the pericardium in seven patients with large effusions of unknown aetiology. Under general anaesthesia the pericardium was approached by the subxiphoid route and drained through a small incision. The sac was then washed with warm saline and refilled. Visual inspection was carried out with both a cystoscope and fibreoptic bronchoscope. The anterolateral aspects of the heart and pericardium were easily seen with the rigid instrument. The fibreoptic scope could be passed around the heart to the posterior pericardium. In five patients otherwise inaccessible invasive tumours were seen and biopsied. Two were bronchogenic, one thymic, one a mesothelioma, and one adenocarcinoma. Two patients had infective effusions, one tuberculous and the other viral. Pericardectomy was carried out under the same anaesthetic in the tuberculous patient. The only adverse effects were ectopic beats when the heart was touched and minor bleeding from the biopsy sites. A pericardial drain was left in situ at the end of the procedure in each case.

In conclusion pericardoscopy provides useful information in patients with pericardial effusion of unknown aetiology who require surgical pericardial drainage.

Left ventricular bands: a morphological study

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Discrete fibromuscular structures crossing the left ventricular cavity (LV bands) were recognised many years ago but recently cross sections echocardiography has resulted in a renewal of interest. It has been suggested that they might be responsible for a variety of problems. To assess their significance we studied autopsy specimens from 636 children's hearts (581 with congenital malformation, 55 normal) and 50 adult hearts with acquired disease. We also studied 159 hearts from six different animal species. LV bands were present in 47·7% of the children's hearts (with no difference in prevalence between the normal hearts and those with congenital malformations) and in 52% of the adult hearts. In 20% of cases with bands the bands were multiple. Almost invariably bands were attached to the septum at one end with the peripheral attachment to either papillary muscle or the ventricular free wall. In animals, bands were present in 100% of sheep, cats, horses, and dogs, in 86% of pigs, and 92% of oxen. A characteristic pattern was present in each species. Left ventricular bands are common and might therefore by chance alone be associated with almost any physical sign or symptom.

Increased prevalence of mitral valve prolapse associated with an elevated type III:III+I collagen ratio

C E Handler, A H Child
Guy's and St George's Hospitals, London

The precise biochemical basis for the mitral valve prolapse syndrome remains unclear. We have assessed the presence of mitral valve prolapse clinically and with phono and M mode and cross sectional echocardiography in 14 female patients (age range 22–57 years) who had joint hypermobility. A raised type III:III+I collagen ratio (range 24–46%, mean 30·7%) (normal 21–23%), measured by a new method using sodium dodecylsulphate polyacrylamide electrophoresis from skin biopsies, was found in all the eight patients samples. An increased aortic wall compliance (100–217%, mean 150·7%) (normal 80–120%), measured by Doppler ultrasound, was found in 13 patients. Nine patients (64%) had mitral valve prolapse, a prevalence at least three times greater than that in the adult population. There was also a trend for an increased prevalence of mitral valve prolapse and higher collagen III:III+I ratios with increasing age.

We conclude that although mitral valve prolapse was not a totally consistent finding an abnormality of collagen biosynthesis may be an important cause of this common cardiac condition.

Br Heart J 1985; **53:** 116–7

Correspondence

Computed tomographic appearances of cardiac amyloidosis

Sir,

T Sekiya *et al* (1984; **51:** 519–22) described the usefulness of computed tomography in differentiating cardiac amyloidosis from both constrictive pericarditis and primary myocardial hypertrophy. Interestingly, they emphasised the radiological features of cardiac amyloidosis: a lower myocardial density on precontrast tomograms with diffuse thickening of the myocardium on postcontrast tomograms. These observations require some comment. Firstly, the inconspicuous diffuse thickening of the left ventricular myocardium is not (as stated in the legend of Fig. 2b) a precontrast but a postcontrast tomogram as indicated by the aortic opacification. Secondly, we completely agree with Dr Sekiya about the mean density value of precontrast computed myocardial amyloid tomograms. We have recently seen a 64 year old woman with systemic amyloidosis that was reactive to a cutaneous fistula of chronic empyema continuously fed by an oesophageal communication. Myocardial density measured by three rectangular regions of 29 pixels each (30·4 (3·4) Hounsfield units (HU)) is comparable to Dr Sekiya's findings (30·6 (3·4) HU) and does not present any overlap with normal myocardial density (Figure). Thirdly, whether or not computed tomography can also differentiate cardiac amyloidosis from other forms of restrictive cardiomyopathy is debatable. It could, however, be suspected that precontrast myocardial density of cardiac haemochromatosis will be different from cardiac amyloidosis density.

Finally, whatever its exact origin—immunogenic or reactive systemic—amyloidosis in western countries is the most frequent cause of restrictive cardiomyopathy. Echocardiography delineates correctly the range of cardiomyopathies. The features of restrictive cardiomyopathy are: (*a*) normal left and right ventricular size, (*b*) thickened walls, (*c*) globally reduced left ventricle, and (*d*) left atrial enlargement (50%) and pericardial effusion (58%).[1] A particular echocardiographic feature indicating the amyloid origin is the granular sparkling appearance of the affected cardiac walls.[1] We believe therefore that echocardiography remains the cornerstone of cardiac amyloidosis diagnosis; in most cases it is the best means of excluding constrictive pericarditis. Nevertheless, the echocardiographic features of cardiac amyloidosis could sometimes be misleading in

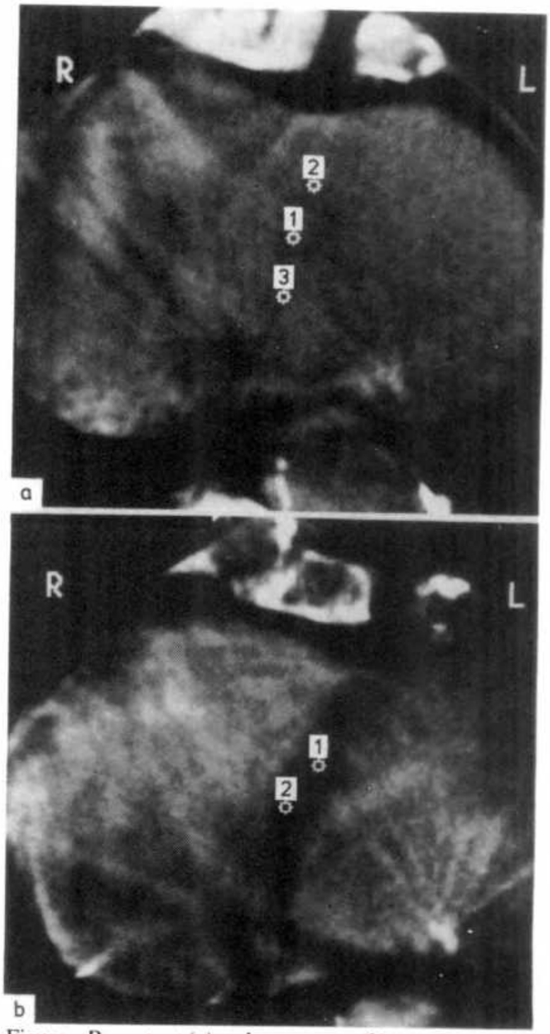

Figure *Precontrast (a) and postcontrast (b) tomograms showing a low septal density before contrast injection. 1, 2, and 3 indicate the three rectangular regions of 29 pixels each.*

patients with hypertrophic cardiomyopathy. In such cases computed tomography may compete with endomyocardial biopsy in providing a correct diagnosis.

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G Kuhn,†
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Route de Lennick 808,
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Reference

1 Siqueira-Filho AG, Cunha CLP, Tajik AJ, Seward JB, Schattenberg TT, Giuliani ER. M-mode and two-dimensional echocardiographic features in cardiac amyloidosis. *Circulation* 1981; **63**: 188–96.

This letter was shown to the authors, who reply as follows:

Sir,
The letter by Drs Depelchin and Kuhn documents an additional case of cardiac amyloidosis, in which the computed tomographic appearances are similar to those in our paper (1984; 51: 519–22). They also correctly point out that the description of a postcontrast computed tomogram was omitted in the legend of Fig. 2b in our report.

I would totally agree with their opinion that computed tomography provides important information for the diagnosis of cardiac amyloidosis but that echocardiography still remains the imaging method of choice in the screening of the disease and in the differentiation of the disease from constrictive pericarditis. Computed tomography would, however, be more useful when echocardiography is technically difficult in patients with obesity or emphysema.

Tohru Sekiya,
Department of Radiology,
Jikei University School of Medicine,
Nishi-Shinbashi,
Minato-Ku,
Tokyo 105, Japan.

Use of the exercise maximal ST segment/heart rate slope in assessing the results of coronary angioplasty

Sir,
We have read with interest the article of Silverton *et al* (1984; **51**: 379–85), which essentially reflects our own opinion, except for a detail which we would like to point out. In fact, we are not convinced that the use of bipolar leads, especially CM5, as proposed by the authors, improves the sensitivity of the test dramatically.

We have recorded routine exercise electrocardiograms in patients before and after transluminal coronary angioplasty. All patients underwent bicycle exercise in the sitting position with monitoring leads V2, V5, and aVF. The signals were digitised and processed for averaging and artefact reduction.

In 40 patients who successfully underwent percutaneous transluminal coronary angioplasty the exercise electrocardiogram correlated well with the angiographic results: mean reduction in the degree of stenosis of 72·4% (range 84·9 to 12·5%; $p<0{\cdot}005$), improvement of maximum predicted heart rate (65·5 (8)% to 82 (8·6)%; $p<0{\cdot}01$), mean exercise time (4·8 (1·8) min to 5·8 (1·4) min; $p<0{\cdot}05$), maximal ergometric load (133 W/2·8 min (18/1·2) to 152 W/3 min (11/1·6); $p<0{\cdot}05$), and maximal rate-pressure product (16·592 (128) to 25·807 (161); $p<0{\cdot}001$). The maximal ST depression at postangiography ergometry fell from 2·8 (1·1) mm to 0·38 (0·06) mm ($p<0{\cdot}01$). In 10 patients in whom transluminal coronary angioplasty was unsuccessful we failed to observe any significant change in the exercise electrocardiogram after operation.

While we agree with Silverton *et al* that exercise testing is of value in the follow up of patients after transluminal coronary angioplasty, we consider that the same good correlations between stenosis reduction and improvement of the exercise electrocardiogram can be obtained with unipolar conventional (V2, V5, aVF) leads.

Leo Finci,
Jean Jacques Goy,
Raymond Maendly,
Milan Grbic,
Ulrich Sigwart,
Division of Cardiology,
Department of Internal Medicine,
Centre Hospitalier Universitaire Vaudois,
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Switzerland.

Br Heart J 1985;53:118

Notices

Intensive care and emergency medicine

The fifth international symposium on intensive care and emergency medicine will take place in Brussels from 26 to 29 March 1985. Further information may be obtained from Dr J-L Vincent, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, B-1070 Brussels, Belgium.

British Cardiac Society

The Annual General Meeting for 1985 will take place in Birmingham on 17 and 18 April 1985, and the closing date for receipt of abstracts will be 8 January 1985.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.

Cardiac pacing and electrophysiology

The Third Asian Pacific Symposium on Cardiac Pacing and Electrophysiology will be held from 27 to 30 October 1985 at the Melbourne Hilton, Melbourne. Further information may be obtained from: Secretary-General, 3rd Asian-Pacific Symposium on Cardiac Pacing and Electrophysiology, Department of Cardiology, Suite 3.5, Epworth Medical Centre, 62 Erin Street, Richmond 3121, Victoria, Australia.

Authors' checklist

The journal is providing a checklist (see p119) for the use of authors preparing articles for possible publication to enable them to ensure that their manuscripts comply with the journal's requirements before submission. Would authors therefore please make a copy of the checklist and send it completed with their manuscripts.

Br Heart J 1985; 53: 119–20

CHECKLIST

Please make a photocopy of this checklist, complete, and send with all manuscripts submitted for publication.

General

☐Two complete sets of the manuscript (including 2 sets of figures) are submitted.

☐The manuscript is typed *treble* spaced throughout on one side only on 22×28 cm (8½×11″) opaque white bond paper with 3 cm margins all around.

☐The manuscript is arranged as follows: (1) title page, (2) summary, (3) text, (4) references, (5) legends, (6) tables. Pages are numbered consecutively, beginning with the title page as page 1.

☐The last name of the first author is typed at the top right corner of each page.

Title page

☐The title and authors' names with symbols (* † ‡ etc) to indicate place of appointment are typed on the title page.

☐Only three authors' names are given for case reports.

☐The name and address of the institutions from which the work originated are included.

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Summary

☐A summary (excluding statistical data) is typed treble spaced on a separate page.

☐The summary is substantive rather than purely descriptive.

☐Abbreviations other than standard units of measurement are not used.

Text

☐Abbreviations or acronyms are always written out in full (for example, ECG, electrocardiogram; LVH, left ventricular hypertrophy; CAD, coronary artery disease, MI, myocardial infarction).

☐Only units of measurement and mathematical formulas and calculations are abbreviated and they follow the form recommended in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (*Br Heart J* 1984; 51: 1–6).

☐Appropriate headings and subheadings are provided.

☐Every reference, figure, and table is cited in the text in numerical order. (Order of mention in text determines the number given to each.)

☐Acknowledgments and details of support in the form of grants, equipment, or drugs are typed at the end of the text, before references.

References

☐References are identified in the text by arabic numerals; no more than three references are cited for any one statement.

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☐Journal references contain *inclusive* page numbers; book references contain *specific* page numbers.

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☐Abbreviations of journals conform to those used in *Index Medicus*, US National Library of Medicine. The style and punctuation of the references follow the format illustrated in the following examples:

Journal: (list *all* authors if six or less; otherwise list first three and add *et al*; do not use full stops after authors' initials)

31 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary

angiographic findings. *Br Heart J* 1984; 52: 304–8.

Chapter in book:

28 Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. *Heart disease in infants, children and adolescents.* Baltimore: Williams and Wilkins, 1968:134–9.

Book (personal author or authors): (all book references should have specific page numbers)

36 Feigenbaum H. *Echocardiography.* 3rd ed. Philadelphia: Lea and Febiger, 1981:549–63.

Figure legends

☐Figure legends are typed treble spaced on sheets separate from the text, and figure numbers correspond with the order in which figures are presented in the text.

☐All abbreviations appearing on the figures are identified at the end of each legend.

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Figures

☐Two sets of unmounted glossy prints (not originals) of each photograph and drawing are submitted in two separate envelopes.

☐Figures, particularly half tones and ECG tracings, have been submitted with the following guidelines in mind: the detail on the figure is sufficiently clear to withstand reduction; the maximum width for one column figures is 7 cm or 2¾" and for two column figures 14 cm or 5¾" maximum; and special features are designated by arrows.

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☐Figures are limited to the number necessary for clarity. (Estimates for colour work will be provided on acceptance of the manuscript for publication. All costs of colour printing will be charged to the author(s).)

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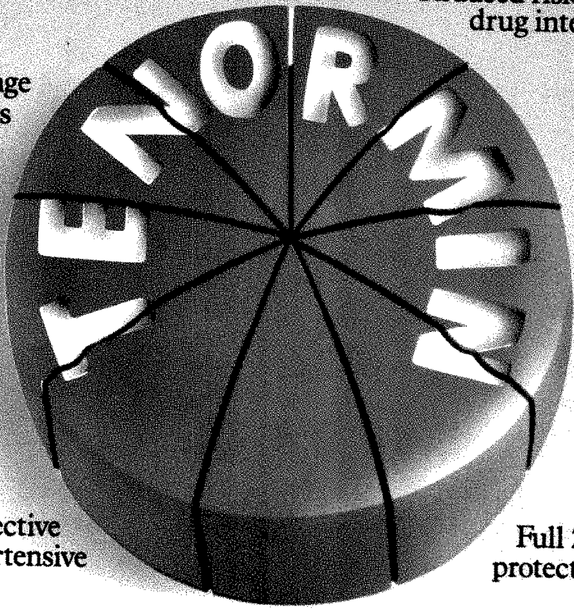

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British Heart Journal

A monthly journal of cardiology published in association with the British Cardiac Society

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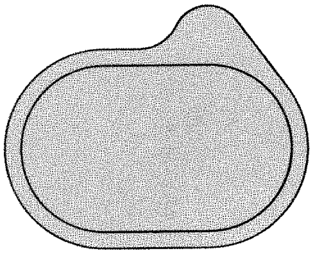

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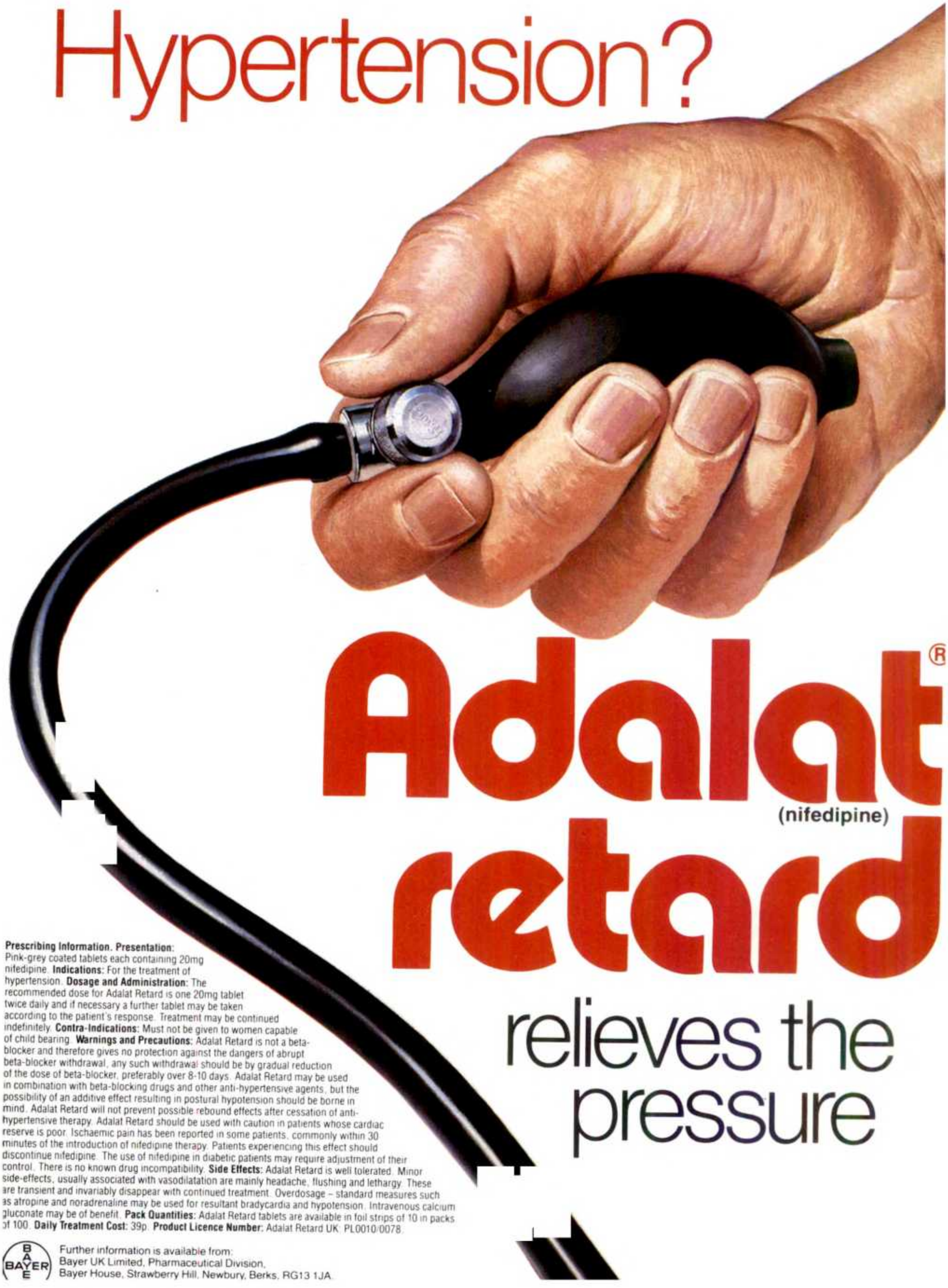

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Br Heart J 1985; **53**: 121–2

Editorial

Stroke distance—an improved measure of cardiovascular function?

D G GIBSON

From the Cardiac Department, Brompton Hospital, London

Over the past few years, methods of measuring cardiac output based on ultrasound techniques have shown considerable promise. These estimates combine the time integral of blood flow velocity, determined by Doppler, with the cross sectional area at the point of measurement.[1–3] The method has been shown to be applicable at several points within the circulation including the atrioventricular valves, the pulmonary valve, and the aortic root or ascending aorta. A number of practical problems remain. It must be assumed that blood flow is laminar. Cross sectional areas estimated by M mode or cross sectional echocardiography are dependent on the resolution of these techniques. The orifice must be assumed to be circular and not to vary during the cardiac cycle, or its geometry must be measured throughout. Despite these limitations, published results indicate that values can be obtained over a wide range from individual patients which agree closely with those derived from established invasive methods.

A new approach to these measurements is put forward in the paper by Haites *et al* in the present issue of this journal (p 123). They have used transaortic velography to determine blood flow velocity and its time integral over systole, which they refer to as stroke distance. They suggest that such measurements may be used to assess cardiac output without conversion to a volumetric measurement or correction for body size. Both stroke distance and minute distance decline during adult life at a rate of approximately 1% a year. Values of both are higher than normal in pregnant women, decreased in patients with hypertension, atrial fibrillation, or cardiac failure, and normal in those convalescing after myocardial infarction. The authors conclude that such measurements constitute a "safe, simple, and physiologically valid way of assessing cardiac output." They also suggest that they may approximate even more closely to stroke index, since the Doppler time integral is multiplied by one quantity with the dimensions of cm^2, aortic cross sectional area, and divided by another, body surface area.

There are several ways in which the suggestions put forward here might have been substantiated. A close correlation between stroke index and stroke distance might have been demonstrated in individual patients; however, no independent measurements of cardiac output were made, although this might have been expected in such a study. It might have been possible to show that the extent of natural variation in a normal population was lower for stroke distance than for other more commonly used measures of flow. This problem has not been specifically addressed, and the use of standard errors rather than standard deviations does not highlight the information. Nevertheless, the 95% confidence limits around the normal populations in Fig. 3 and 4 (p 126) are substantial, and at first sight do not seem to be significantly less than those around cardiac or stroke index. The suggestion is also made that aortic cross sectional area reflects body size and metabolic requirements better than surface area. Again, no data are presented to support this hypothesis, and measurements in published reports lend no support to it. Even during the period of growth when correlation between aortic size and body surface area would be expected, directly measured confidence limits are wide, the 95% limits for aortic dimension being 16% in the study of Henry *et al*,[4] corresponding to a 30% variation in area. That demonstrated by Rogé *et al* is even larger,[5] the 90% limits being approximately 30% in dimension at a body surface area of 1·5 m^2, corresponding to a range of area of more than 50%. There seems to be no reason to suppose that these limits would be any narrower in disease or that they would be reduced if

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"metabolic requirements" were taken into account. Thus, although the authors' thesis that stroke index and stroke distance both have the same units—length—is correct, this dimensional equivalence is not accompanied by corresponding biological significance.

While the positive findings in the different patient groups in this study are of interest, they are not specific. In the present series, stroke distance fell with age; this might have been due to a reduction in stroke index or to an increase in aortic cross sectional area. In hypertensive patients, particularly when some are receiving treatment with beta blocking drugs, a variety of mechanisms can be invoked, including depression of ventricular function, increased afterload, sympathetic inhibition, and increase in cardiac output in the early stages of the disease, so that any value of stroke distance can be explained, whether high, normal, or low. Similar considerations apply for patients with atrial fibrillation of differing aetiology or for an unselected group after myocardial infarction, where low as well as normal values could be accounted for with equal facility. Stroke distance seems to have much in common with other measurements such as arteriovenous oxygen difference or even circulation time, which are likely to have varied in a similar manner as stroke index in the patients studied. These all share the disadvantage that when values occur outside the expected range the underlying mechanism is never clear.

In summary, I consider that measurements of cross sectional area should continue to be made in association with estimates of blood flow velocity. In this way stroke volume and cardiac output can be obtained, which are recognised variables describing circulatory function and which can be estimated and correlated with more direct measurements. Failure to determine aortic root area will introduce a major additional source of variance in the relation between stroke distance and stroke volume index, which could readily be avoided by simple echocardiographic measurements. The case for considering stroke or minute distance as equal or even superior to current measurements of blood flow remains unproved.

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Br Heart J 1985; 53: 123–9

Assessment of cardiac output by the Doppler ultrasound technique alone

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SUMMARY The normal range of aortic blood velocity was established in 140 healthy adults, using a non-invasive Doppler ultrasound technique. Integration of the area under the velocity-time curve for each heart beat gave stroke distance, which, when multiplied by heart rate, gave minute distance. Stroke distance and minute distance are an indication of stroke volume and cardiac output respectively and both show a progressive decline with age of about 1% per annum of adult life. Stroke distance gave the greatest discrimination between patient groups and, compared with age corrected normal values, was increased by 43% in 12 pregnant women, normal in 16 patients convalescing after myocardial infarction, and decreased by 14% in 15 patients with hypertension, by 31% in 12 patients with atrial fibrillation, and by 43% in 13 patients with cardiac failure.

Measurement of aortic blood velocity and its derivatives alone, without determination of aortic size, is a safe, simple, and physiologically valid way of assessing cardiac output.

Cardiac output is the ultimate expression of cardiovascular function, yet we learn little about either from clinical examination. Even the physical signs attributed to cardiac failure are not pathognomonic of impaired cardiac function but may also be found when the heart is functioning normally with volume overload of the circulation. In a whole variety of clinical situations there is therefore a need to be able to assess cardiac output, but until now there has not been a satisfactory non-invasive method.

The Doppler ultrasound technique offers the possibility of a simple to use, non-invasive bedside method of measuring cardiac output, giving absolute values of blood flow for a modest capital outlay and low running cost. Blood velocity is determined ultrasonically at a point in the circulation where the cross sectional area may be measured. Three sites have been described: the mitral valve orifice,[1] the root of the aorta,[2] and the aortic arch.[3 4] Integration of the area under the velocity-time curve for each heart beat gives a distance that, if multiplied by the cross sectional area at the point of measurement of velocity, gives stroke volume. When the measurements are made in the aorta there are several assumptions implicit in the calculation: non-turbulent flow with a flat velocity profile, constant aortic diameter throughout systole, and total stroke volume passing the point of velocity measurement. If velocity is measured in the aortic root no allowance is made for flow to the coronary arteries or to the head and neck if the measurement is made in the aortic arch. The most difficult part technically is measurement of aortic cross sectional area, but even with satisfactory measurements volumetric cardiac output may be considerably overestimated.[5]

The technique we describe uses blood velocity measurements alone without estimation of cross sectional area. The arch of the aorta is used, where a flat velocity profile is a reasonable assumption,[6] and blood flow is less likely to be turbulent than in the aortic root,[7] although a substantial and unknown proportion of stroke volume has left the aorta by the time it reaches the point where velocity is measured. Clinical experience suggests, however, that measuring the cross sectional area is unnecessary for converting the velocity-time integral into a volume, the velocity measurements by themselves closely reflecting cardiac output. This is fortunate as velocity measurements may be made with ease even in very sick patients, whereas measurement of the cross sectional areas of either the aorta or mitral valve may be technically difficult in a substantial proportion of subjects. If velocity measurements are used by themselves to assess

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cardiac output none of the assumptions mentioned above need be made. Velocity alone may be measured with equipment used by relatively unskilled staff whereas if combined with measurement of cross sectional area it is best done with a cross sectional echocardiograph with a Doppler mode. Such equipment is commercially available and may give accurate values for volumetric cardiac output[8 9] but is much more expensive and less portable than instruments measuring velocity alone, which have been used in conjunction with echocardiography.[10 11] Considerable skill is required to get good quality cross sectional echocardiograms for the measurement of cross sectional areas, and, because the equipment is multipurpose, it is less likely to be available for repeated measurements at the bedside of a sick patient.

Reproducibility of the technique of transcutaneous aortovelography described here is good, with a 6·6% deviation from exact agreement with one operator and one of 7·3% between operators.[12] While a satisfactory study showing correlation between aortovelography and cardiac output measurement has yet to be reported, several comparisons have been made between aortovelography and cardiac output measured by thermodilution or dye dilution, which show close proportionality between changes in aortovelographic variables and changes in cardiac output.[13-15]

The safety and ease of use of the technique of transcutaneous aortovelography makes the assessment of cardiac output feasible in a wide range of situations, but validation is needed by direct comparison between aortovelography measurements and cardiac output and by performing aortovelography in patients known to have normal and abnormal cardiac outputs. We have previously reported the range of aortic blood velocity in normal subjects and shown that it is independent of sex, body surface area, and blood pressure but declines progressively with age.[16] We report results from normal subjects, pregnant women, and patients with hypertension, myocardial infarction, atrial fibrillation, or cardiac failure.

Subjects and methods

NORMAL SUBJECTS

One hundred and seventy five apparently healthy staff and patients attending a general practice surgery were initially selected, but 35 were excluded after a medical history, physical examination, and electrocardiography because of known or suspected heart disease, hypertension, thyroid disease, concurrent drug treatment, or recent intercurrent disease. The remaining 140 subjects ranged in age from 16 to 74 years with a balanced representation of all ages and both sexes.

PREGNANT WOMEN

This group comprised 12 healthy women with a mean duration of pregnancy of 18·6 weeks and a mean age of 29 years.

PATIENT GROUPS

Hypertension—In the search for normal subjects 15 patients with known or newly diagnosed essential hypertension were identified (mean age 53 years). Their mean blood pressure was 165/103 mm Hg compared with the age corrected value of 136/83 mm Hg in the normal subjects. Six were receiving no treatment, five were taking beta blockers, two with the addition of a diuretic, and four were taking a diuretic alone.

Cardiac failure—Thirteen patients with cardiac disease were studied (mean age 57 years) who were admitted to hospital with clinical signs of right, left, or biventricular failure for which they were still requiring treatment.

Myocardial infarction—Sixteen patients recuperating from acute myocardial infarction within the previous 10 days were studied shortly before discharge from hospital. None had clinical evidence of cardiac failure at the time of aortic blood velocity measurements. The mean left ventricular ejection fraction of eight patients from this group was normal at 0·62 when measured at rest by a radionuclide method.

Atrial fibrillation—Twelve patients (mean age 64 years) were studied: three had mitral valve disease, five ischaemic heart disease or hypertension, one treated thyrotoxicosis, and three unexplained atrial fibrillation. None was taking diuretics or had a history of cardiac failure, eight were taking digoxin, and one amiodarone for the control of ventricular rate.

AORTIC BLOOD VELOCITY MEASUREMENT

In subjects in sinus rhythm aortic blood velocity was recorded over 10 cardiac cycles using the Transcutaneous Aortic Velograph (TAV) Type 1006 (Muirhead Medical Ltd), a restyled version of the equipment described by Sequeira and colleagues.[13] The recording was made with the subject supine after five minutes' rest. Longer recordings of up to 200 complexes were recorded from patients with atrial fibrillation as part of another study.

A transducer, emitting continuous wave ultrasound at 2 MHz, is held in the suprasternal notch and directed at the arch of the aorta. The same transducer detects back scattered ultrasound which generates Doppler shift frequencies proportional to the velocities of blood in the ultrasound pathway. The results of spectral analysis of the Doppler frequencies are displayed on a paper trace, which may be directly calibrated as aortic blood velocity against time. Angulation of the transducer is not critical, and help in

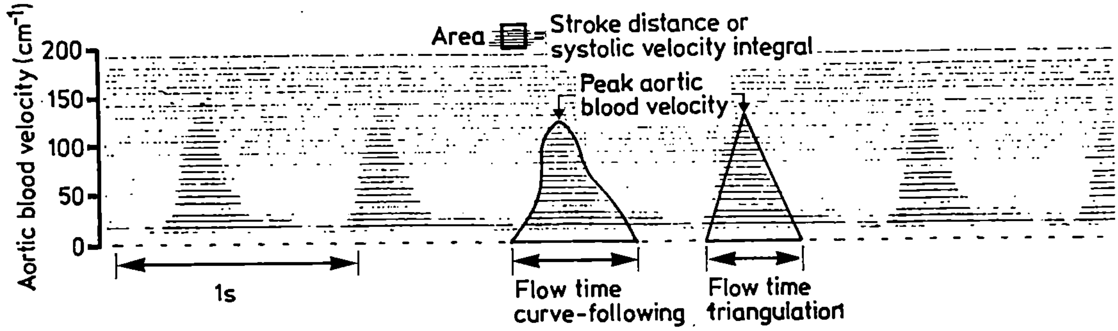

Fig. 1 *A typical aortovelography trace showing measurement of stroke distance by curve-following and triangulation.*

positioning it is obtained by maximising the pitch of the Doppler frequencies played through a loudspeaker, at which point the ultrasound beam is in line with the direction of blood flow.

INTERPRETATION OF VELOCITY MEASUREMENT

Fig. 1 shows a typical trace. The outline of the velocity-time complex represents the highest velocity recorded in the ultrasound path at any instant. The complexes are approximately triangular, and the apex represents peak aortic blood velocity occurring in aortic midstream in midsystole, and the length of the base of the triangle represents the duration of left ventricular ejection, or flow-time. The area within the velocity-time complex is dimensionally a distance and is recorded in centimetres as "stroke distance," analogous to stroke volume. Stroke distance multiplied by heart rate in beats per minute gives "minute distance," analogous to cardiac output. The velocity-time complex is not exactly triangular, with some rounding of the apex and non-linearity of leading and trailing edges. In our normal subjects we compare two methods of calculating stroke distance, by measuring the base and height of a superimposed best fit triangle, and by a curve-following programme with a digitiser and computer. Triangulated measurements of stroke distance were used in patients with atrial fibrillation and their controls; in other groups the results were calculated by curve-following. Measurements from 10 consecutive complexes were averaged in sinus rhythm, but up to 200 complexes were averaged in atrial fibrillation.

STATISTICAL METHODS

Blood velocity measurements in five patient groups were compared with predicted means and their residual standard deviations, obtained from the normal series by using the mean ages of the patient groups in the linear regression equations for stroke distance and minute distance against age. Unpaired *t* tests were used for comparison of means which are given with 1 standard deviation.

Results

STROKE DISTANCE BY TRIANGULATION AND CURVE-FOLLOWING

In 140 healthy subjects the mean peak aortic blood velocity was 102 cm s^{-1} as measured by a curve-following programme with a digitiser. This was overestimated by 14% by triangulation, but triangulation slightly underestimates stroke distance, with mean stroke distances of 19·4 and 19·7 cm by triangulation and curve-following respectively. For practical purposes either method may be used to measure stroke distance, depending on the availability of digitising equipment, the close agreement between these two methods of measurement being shown in Fig. 2.

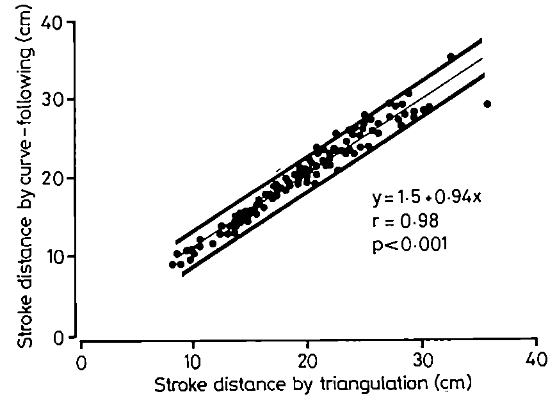

Fig. 2 *Stroke distance measured by curve-following and by triangulation. The regression line and 95% confidence limits are given for data from 140 normal subjects.*

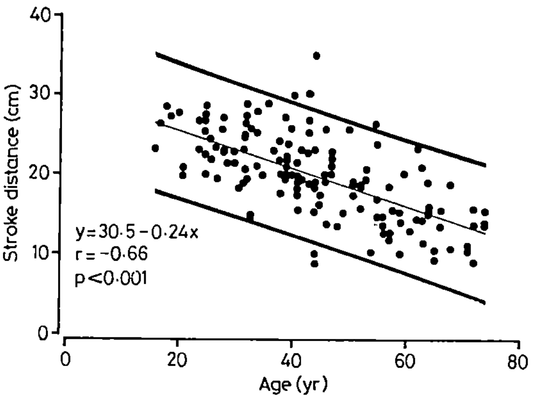

Fig. 3 *Regression of stroke distance on age. The regression line and 95% confidence limits are given for data from 140 normal subjects.*

Normal subjects

Figs. 3 and 4 show the 95% confidence limits for the decline of stroke distance and minute distance with age. Both measurements fall by about 45% between the ages of 20 and 70 years. The systolic-velocity integral or stroke distance is highly correlated with peak aortic velocity (r=0·91, p<0·001) but not with flow-time (r=0·08, 0·02<p<0·4), indicating that in normal subjects changes in stroke distance are brought about by variation in blood velocity rather than in ejection time.

Patient groups

Fig. 5 shows the mean values of stroke distance and minute distance in pregnancy, hypertension, cardiac failure, myocardial infarction, and atrial fibrillation compared with age corrected normal values. Peak aortic blood velocity and flow time, the apex and base of the triangular velocity-time complex, though not correlated with each other in normal subjects, are nevertheless altered in the same direction in different patient groups. Stroke distance, the area of the complex, being closely related to the product of peak aortic blood velocity and flow-time, shows a greater separation between groups than either of these measurements. Since a reduced stroke volume or stroke distance will lead to an increased heart rate and a proportionately smaller reduction in cardiac output minute distance therefore shows less discrimination between groups than stroke distance.

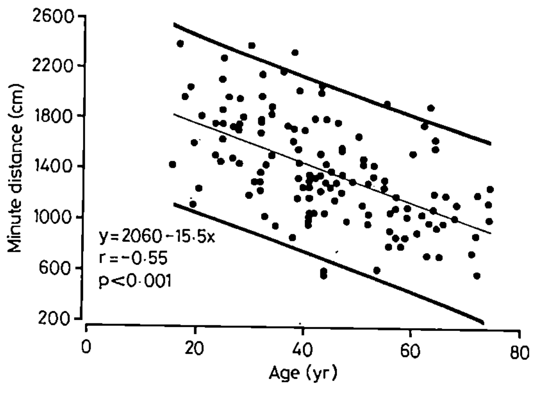

Fig. 4 *Regression of minute distance on age. The regression line and 95% confidence limits are given for data from 140 normal subjects.*

Pregnancy—In pregnancy there is a 43% increase in stroke distance (p<0·001) resulting from a 30% increase in peak aortic blood velocity (p<0·001) and a 12% increase in flow-time (p<0·01). Minute distance shows an even greater increase over normal at 56% (p<0·001) since mean heart rate is five beats per minute faster in pregnancy (0·1<p<0·2).

Hypertension—Although neither peak aortic blood velocity or flow time are significantly reduced, stroke distance and minute distance are 13% and 15% lower

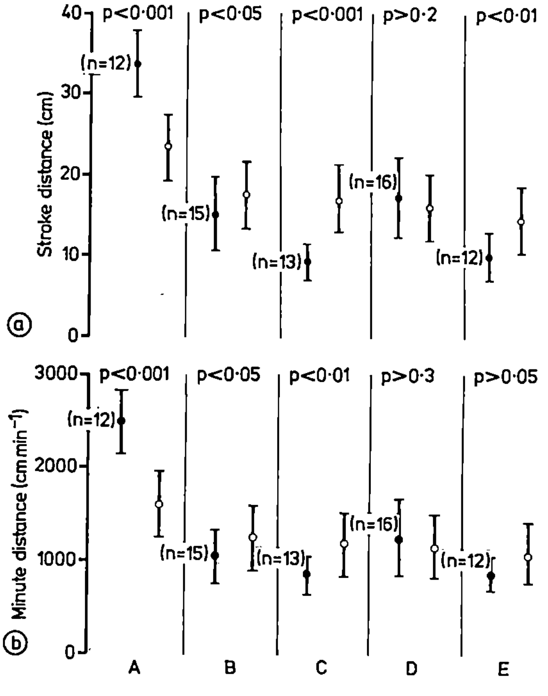

Fig. 5 *(a) Mean (SD) stroke distance and (b) mean (SD) minute distance compared with age corrected normal (○) values (n=140) in five patient groups (●): (A) pregnancy (mean age 29 yr); (B) hypertension (mean age 53 yr); (C) cardiac failure (mean age 57 yr); (D) myocardial infarction (mean age 60 yr); (E) atrial fibrillation (mean age 64 yr).*

than normal respectively ($p<0.05$). The number of subjects in this group is too small to enable us to say whether this reduction in cardiac output is due to hypertension itself or its treatment.

Cardiac failure—Peak aortic blood velocity and flow time are reduced by 23% and 25% leading to 43% reduction in stroke distance. Heart rate is significantly increased by 20 beats per minute to 90 beats/min ($p<0.001$), compensating to some extent for the reduced stroke distance, minute distance being reduced by 28%.

Myocardial infarction—Aortic blood velocity and its derivatives were normal in this group of convalescent patients.

Atrial fibrillation—Peak aortic blood velocity and flow time are both reduced by 17% leading to 31% reduction in stroke distance. Ventricular rate is significantly increased to 87 beats per minute ($p<0.001$), compensating partially for the reduced stroke distance, minute distance being reduced but not significantly.

Discussion

Cardiac output is the ultimate expression of cardiovascular function, so it is surprising that its measurement is made so seldom in clinical practice. This relates to difficulties of measurement but also to its interpretation. Volumetric cardiac output has to be corrected for variation in body size and by convention this is done by division with an estimate of body surface area, even though the statistical basis for this manoeuvre is suspect, and the correction breaks down in neonates.[17] Cardiac output diminishes with age,[18] but there are no generally accepted normal values which take age into consideration.

Another problem is that homeostatic mechanisms seek to stabilise cardiac output, the most important of these being alteration of heart rate. Cardiac output per beat, or stroke volume may therefore be a more fundamental expression of cardiovascular function, and that too is usually corrected for body size by division by body surface area. By dimensional analysis, volume/area=distance and stroke volume/body surface area=stroke volume index, the latter therefore being a linear measurement of distance.

Non-invasive measurement of cardiac output by combined Doppler and echocardiography depends on measurement of the systolic velocity integral, or stroke distance, and the cross sectional area at the point where the velocity measurement is made. The systolic velocity integral is then multiplied by the cross sectional area to give stroke volume. The relation between stroke volume and stroke distance measured in the aorta is thus approximately as follows: stroke volume/aortic cross sectional area=stroke distance. Put in this way we see the close analogy between stroke volume index and stroke distance. Both are unidimensional and corrected for variation in body size, the former by body surface area and the latter by aortic cross sectional area, which may reflect body size and metabolic requirements rather better than body surface area. Having measured stroke distance directly we consider it unnecessary to convert it to a volumetric measurement by multiplication with aortic cross sectional area only to correct for body size by dividing arbitrarily by another area, that of the body surface.

If stroke distance is biologically corrected for body size there should be no correlation with body surface area, which is indeed the case,[16] and aortic blood velocity might be expected to have a similar value throughout infancy and childhood, which is also true,[19] which cannot be said of the cardiac index.[20 21]

These results indicate that once a normal range of values is established, aortic blood velocity measurements may be used by themselves to assess cardiac output without conversion to a volumetric measurement or correction for body size. The pronounced decline of aortic blood velocity and its derivatives with age means that age correction is necessary, however, but prediction of mean values at any adult age under 75 years is readily done from our data using the regression equations relating velocity measurements to age.

There are two possible reasons for the reduction of aortic blood velocity and its derivatives with age: reduction of cardiac output and enlargement of the aorta. Volumetric cardiac output decreases by about 1% per annum between the ages of 20 and 80,[18] a comparable figure to the decline of minute distance of 0·88% a year in our series. Furthermore, during adult life there may be some passive dilatation of the aorta, but evidence on this point is scanty. One source reports an increase in external aortic diameter of 0·75% a year.[22]

In pregnancy, an increase in both stroke volume and heart rate contribute to an increased cardiac output of about 40% in mid-trimester.[23] Our finding of a 56% increase in minute distance is a higher percentage increase than has been recorded for cardiac output, but we have confirmed this finding in a separate group of patients at an earlier stage of pregnancy.

In the early stages of hypertension cardiac output may be raised, but later with increasing peripheral resistance it falls below normal.[24] Treatment either with beta blockers or diuretics may also cause a reduction of cardiac output,[25 26] so our finding of a significant reduction of minute distance in the hypertensive group is not unexpected.

The definition of cardiac failure is elusive,[27] but it has long been known that cardiac output is reduced in the syndrome of congestive cardiac failure, although there is some overlap with the range of values found in normal subjects.[28] In our patients with cardiac failure, the mean values of aortic blood velocity and its derivatives were all significantly reduced. Stroke distance showed the greatest percentage reduction, an increased heart rate providing partial compensation leading to a smaller proportional fall in minute distance. As might be expected, the range of values for stroke distance found in cardiac failure overlapped with normal age corrected values, but its measurement gives an indication of the severity of cardiac dysfunction that is not available from the clinical examination.

At the time of discharge all aortic blood velocity measurements were normal in the patients with myocardial infarction that we studied, who had had an uncomplicated course with no clinical evidence of cardiac failure and, where measured, normal left ventricular ejection fractions. Stroke volume and cardiac output have been measured in patients with myocardial infarction,[29] and while stroke volume and often cardiac output were diminished on the first days after infarction, both were normal by the time of discharge from hospital.

In atrial fibrillation, loss of atrial function leads to reduction of stroke volume and cardiac output.[30 31] Our results show a 31% reduction of stroke distance in atrial fibrillation with a 19% reduction of minute distance, which does not, however, achieve statistical significance. The increased ventricular rate in atrial fibrillation compensates for the fall in stroke volume and may well be under automatic control, especially in patients taking digoxin.[32] Measurement of cardiac output in atrial fibrillation could bring a new precision to the control of the ventricular rate: the optimum rate is that which results in a normal cardiac output.

The non-invasive assessment of cardiac output by aortic blood velocity measurements by themselves has given results that are wholly consistent with previously published work where cardiac output has been measured by conventional invasive techniques. Because of the safety and acceptability of the method it is possible to collect a large series of results from normal subjects to compare with those from patients of any age, in whom it is now feasible to make frequent sequential measurements at the bedside or in the outpatient clinic. Cardiac output is such an important haemodynamic variable that its more frequent measurement—and a greater understanding of the factors that influence it—must lead to improved patient care.

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Doppler echocardiographic measurement of cardiac output using the mitral orifice method

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SUMMARY Cardiac output was determined in 20 patients with various cardiac conditions by measuring the cross sectional area of the mitral orifice by echocardiography and the transmitral flow by the Doppler technique. Cardiac output was calculated by multiplying the corrected mitral orifice area by the maximum diastolic velocity integral recorded by the pulsed mode. The results were compared with that obtained by the Fick method. The correlation for cardiac output by the two techniques was high in the whole group, particularly in patients without mitral regurgitation. There was also a good correlation for stroke volume determined by the two methods. Cardiac output was significantly overestimated by the continuous mode and in patients with mitral regurgitation. These results show that the mitral orifice method provides a new and reliable approach to the non-invasive measurement of cardiac output.

With the advent of Doppler echocardiography there has been an increased interest in estimating cardiac output by measuring aortic flow.[1 2] Although satisfactory results have been reported using different models, the true value of determining the aortic cross sectional area method remains in dispute. This technique is invalid in patients with an abnormal aortic valve.[3–6] An alternative approach to estimating cardiac output is to measure blood flow through the mitral orifice. Preliminary results obtained in animal experiments have been promising.[7] There have, however, been few clinical studies using this approach. We therefore undertook the present study to evaluate the feasibility and validity of this method in clinical practice.

Patients and methods

STUDY POPULATION

Twenty consecutive patients (11 men and nine women, ranging in age from 17 to 65 years) were studied. All patients gave their informed consent to participate in the study and underwent right heart catheterisation with measurement of cardiac output by the Fick method. The Table shows the clinical diagnoses. All patients were in sinus rhythm. Doppler echocardiography and right heart catheterisation were performed within 24 hours by different investigators, and the results were not compared until after the study was completed.

THEORETICAL CONSIDERATIONS

Transmitral flow (MF) can be calculated as: $MF=\int \bar{V}(t)\ CSA(t)\ dt$ where $\bar{V}$ is the spatial mean blood velocity, CSA is the cross sectional area of the mitral orifice, and t indicates that both $\bar{V}$ and CSA are functions of time.

The maximal mitral orifice area can readily be measured from the parasternal left ventricular short axis view. Since the mitral orifice area, however, changes considerably during diastole the maximal area must be corrected for such variations. Assuming that the normal mitral valve orifice varies throughout diastole as a series of ellipses, the changes of the mediolateral diameters of these ellipses are so small relative to those of anteroposterior diameters that these changes can be ignored. In such circumstances, the changes in area will be directly proportional to changes in anteroposterior diameter, which are shown on the derived M mode echocardiograms. By this technique, we can obtain a ratio of the mean to maximal opening of the mitral orifice. This ratio multiplied by the maximal mitral orifice area equals the mean or

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Table *Results of Doppler echocardiography in 20 patients*

Case No	*Diagnosis*	*MMA* (cm^2)	*MOR*	*CMA* (cm^2)	*DVI (cm)*	*HR(D) (beats/min)*	*SV(D)* (cm^3)	*CO(D) (l/min)*
1	CAD	9·58	0·55	5·27	17·1	55	90	5·0
2	Normal	6·98	0·61	4·26	24·7	96	105	10·0
3	CAD	4·65	0·72	3·35	20·8	90	70	6·3
4	PS	8·38	0·57	4·78	23·5	58	112	6·5
5	CAD	8·95	0·52	4·65	19·5	48	91	4·4
6	HCM	6·50	0·80	5·20	16·4	62	85	5·3
7	CAD	9·16	0·52	4·76	18·2	47	87	4·1
8	Normal	7·42	0·62	4·60	17·6	75	81	6·1
9	CAD and VA	9·82	0·57	5·60	14·2	63	80	5·0
10	MR	9·72	0·63	6·12	19·6	70	120	8·4
11	AV	7·11	0·57	4·05	19·4	98	79	7·7
12	PE	10·60	0·65	6·89	15·1	80	104	8·3
13	Normal	9·44	0·58	5·48	24·0	60	132	7·9
14	HCM	7·48	0·80	5·98	11·9	73	71	5·2
15	CAD and VA	8·26	0·51	4·21	25·6	50	108	5·4
16	CAD, VA, and MR	11·02	0·54	5·95	17·4	55	104	5·7
17	ASD	6·80	0·78	5·30	15·7	73	83	6·1
18	PS	7·77	0·60	4·66	18·7	67	87	5·8
19	PS	7·27	0·70	5·09	18·9	75	96	7·2
20	ASD	7·28	0·65	4·73	16·0	70	76	5·3

CAD, coronary artery disease; PS, pulmonary stenosis; HCM, hypertrophic cardiomyopathy; VA, left ventricular aneurysm; MR, mitral regurgitation; AV, prosthetic aortic valve; PE, pericardial effusion; ASD, atrial septal defect; MMA, maximal mitral orifice area; MOR, mitral orifice opening ratio; CMA, corrected mitral orifice area; DVI, diastolic maximum velocity integral recorded from position A by pulsed Doppler; HR(D), heart rate during Doppler examination; SV(D) and CO(D), stroke volume and cardiac output by Doppler echocardiography.

corrected mitral area, which can then be regarded as a constant during diastole.

The Doppler mean velocity is representative of the spatial mean velocity of the whole mitral orifice area only if the blood velocity profile is flat. Experimental data indicate that the velocity profile across the mitral valve is flat except for a zone of high shear near the margin of the anterior leaflet in mid and end diastole.[8] To our knowledge, there is no such information available in humans. Assuming that there is a flat velocity profile across the mitral orifice during diastole and the angle between the ultrasound beam and the blood flow direction is 0°, the transversed distance of blood can be obtained by integrating the velocity during diastole. Cardiac output (CO) can then be calculated as: $CO = DVI \times CMA \times HR$, where DVI is the diastolic velocity integral, CMA the corrected mitral orifice area, and HR the heart rate.

ECHOCARDIOGRAPHY

A phased array cross sectional instrument (IREX III) with a 2·5 MHz transducer was used for both cross sectional imaging and M mode recordings. All patients were examined in the left lateral decubitus position. After the mitral valve orifice had been imaged in the left parasternal short axis view, the transducer was angled to record the maximal mitral orifice area and both leaflet tips. The images were recorded on video tapes. By adjusting the M mode cursor across the middle of the mitral valve orifice, a derived M mode echocardiogram was obtained at a paper speed of 50 mm/s.

DOPPLER TECHNIQUE

A commercially available multifrequency (1–10 MHz) Doppler instrument (ALFRED, Vingmed), with both pulsed and continuous mode, and a transducer of 2 MHz were used to record the Doppler signals. The instrument has been described in detail elsewhere.[6] The sample volume in the pulsed mode is approximately 8 mm in diameter and 5 mm in length. The received signals were processed by two frequency estimators and converted into analogue voltages in proportion to the mean and maximum Doppler frequency shifts. The electrocardiograms, the mean and maximum velocity curves, the phonocardiograms, and the amplitude of the Doppler signals were recorded simultaneously on a Mingograph 82 electrocardiograph (Siemens Elema) at a paper speed of 50 mm/s.

The Doppler probe was placed at the apex, and the continuous mode was first used to localise and record the mitral flow signals. The probe was angled by listening to the audio signals to obtain the highest mitral flow velocity. The pulsed mode was then switched on to record the velocities from different positions: (A) where the mitral valve opening was first heard and recorded on the amplitude curves, (B) 1 cm above (A), and (C) where only the mitral valve closure was heard and recorded. Care was taken to adjust the gain setting properly to minimise noise interference and to avoid the left ventricular outflow area while still maximising mitral flow.

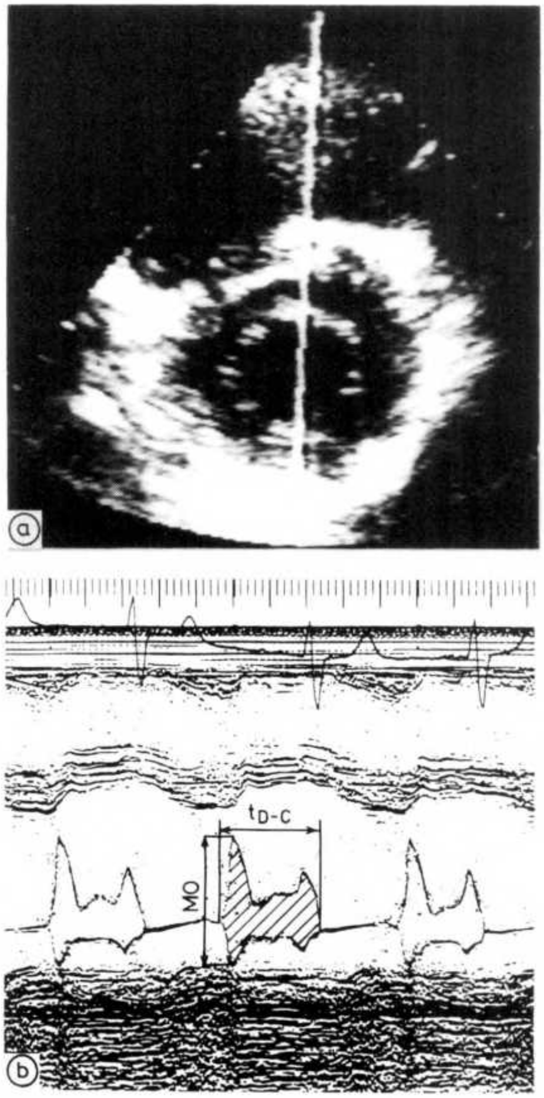

Fig. 1 *(a) Short axis echocardiogram showing the maximal mitral valve orifice area and the position of the M mode line. (b) A derived M mode echocardiogram showing the method for calculating the mitral orifice opening ratio. The area between the leaflets was integrated and divided by the time interval between D and C points (t_{D-C}) to obtain the mean opening which, divided by the maximal opening (MO), equals the opening ratio.*

DATA ANALYSIS

The video tape recordings were analysed frame by frame. The frame with the maximal mitral orifice area within one cardiac cycle was selected and digitised by a computer system (CARDIO 80, Kontron) programmed to give a planimetered area. Five to seven consecutive cardiac cycles were analysed and the values averaged (Fig. 1).

The derived M mode echocardiograms were traced manually along the outermost echoes from the mitral valve and digitised by the same computer to determine the following measurements: (*a*) the opening area enclosed by the two leaflets; (*b*) the time interval between the D and C points of the mitral valve; (*c*) the mean opening of the two leaflets, which was obtained by dividing (*a*) by (*b*); (*d*) the maximal opening, which corresponds to EE′ or AA′ depending on which is the larger; and (*e*) the mean to maximal opening ratio, which was obtained by dividing (*c*) by (*d*). Ten consecutive cardiac cycles were digitised and the mean opening ratio calculated (Fig. 1).

The diastolic velocity integral was determined by tracing and digitising the area under the mitral flow velocity curves over 10 cardiac cycles. Since maximum velocities are less affected by errors in aiming than mean velocities[6 9] we integrated the maximum velocity curves. The integration was ended at the mitral valve closure component of the first heart sound, which was identified by the recordings at position C. The mitral velocity recorded at position A was used to calculate cardiac output (Fig. 2).

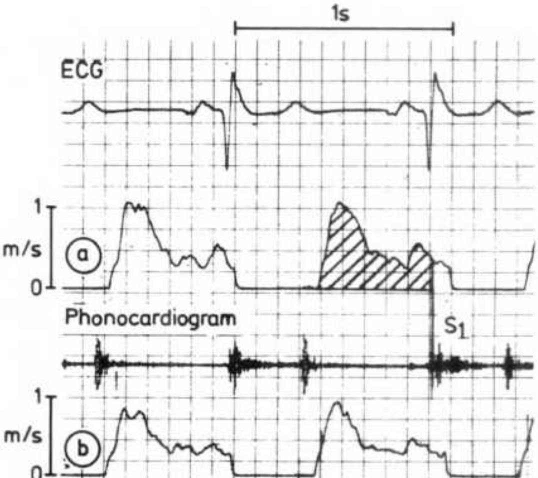

Fig. 2 *Electrocardiogram (ECG), phonocardiogram, and pulsed Doppler recordings showing (a) the maximal and (b) mean velocity, (c) the amplitude of Doppler signal, and the technique of integrating the maximum velocity (hatched area).*

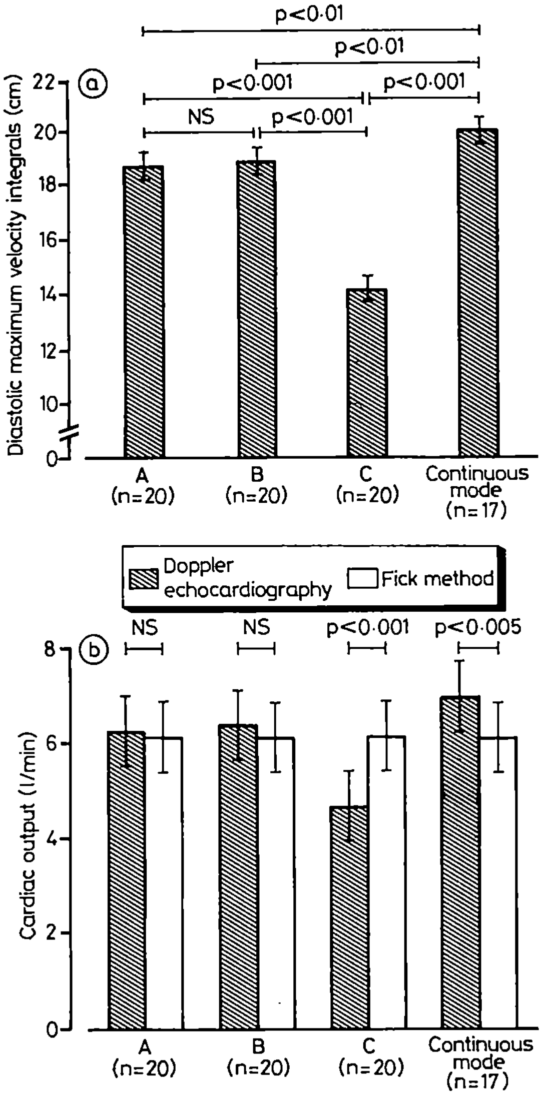

Fig. 3 *(a) Diastolic velocity integrals recorded by the pulsed mode Doppler technique from different positions (A, B, and C) and by the continuous mode. (b) Cardiac output determined by Doppler echocardiography using different diastolic velocity integrals and by the Fick method. Values are mean (SD).*

FICK METHOD

Cardiac output was measured in the catheterisation laboratory using the standard Fick method. Oxygen in air and blood was measured using ABL-3 and OSM-3 instruments (Radiometer, Copenhagen) respectively. Stroke volume was computed by dividing cardiac output by heart rate measured during the Fick procedure.

STATISTICS

Statistical analysis was performed using paired *t* tests and correlation and linear regression analysis. All results are given as mean and 1 standard deviation (SD).

Results

DOPPLER ECHOCARDIOGRAPHY

The Table shows the individual results of Doppler echocardiography. Technically adequate recordings of cross sectional and M mode echocardiograms were obtained in all patients. The values for the maximal mitral orifice area varied between 4·65 and 11·02 cm^2 (8·21 (1·57) cm^2). The smallest value was found in one patient with coronary artery disease (case 3), who also had the lowest stroke volume by Doppler echocardiography. The largest value was found in one (case 16) of the two patients with mitral regurgitation, both of whom were characterised by a high stroke volume by Doppler echocardiography. The values for the mitral orifice opening ratio varied between 0·51 and 0·80 (0·62 (0·09)). The highest values were found in two patients with hypertrophic cardiomyopathy (cases 6 and 14), which was related to the reduced EF slope in these patients. The corrected mitral orifice area ranged from 3·35 to 6·89 cm^2 (5·05 (0·82) cm^2). The smallest value was found in the patient with the smallest maximal mitral orifice area and the largest value in the patient with a pericardial effusion (case 12).

All Doppler measurements recorded in the pulsed mode were technically adequate, whereas recordings in the continuous mode from three patients were excluded because of noise interference. With the pulsed mode, the diastolic velocity integral from position A ranged from 11·9 to 25·6 cm (18·7 (3·61) cm). There was no significant difference between the velocity integral measured from positions A and B, whereas the velocity integral recorded from position C was significantly lower than that from position A ($p<0·001$) or B ($p<0·001$). On the other hand, the velocity integral recorded by the continuous mode was significantly larger than that recorded from any of the three positions by the pulsed mode (Fig. 3).

The cardiac output by Doppler echocardiography using the pulsed mode and the diastolic velocity integral from position A ranged from 4·4 to 10·0 l/min (6·3 (1·5) l/min). The stroke volume varied between 70 and 132 cm^3 (93 (17) cm^3). The comparison between the maximal mitral orifice area and the stroke volume yielded a significant correlation ($r=0·54$, $p<0·02$), although the values were scattered. There was no significant correlation between the corrected mitral orifice area and the stroke volume ($r=0·33$, $p>0·05$). The correlation between the diastolic velocity integral and the stroke volume was also significant ($r=0·66$, $p<0·005$).

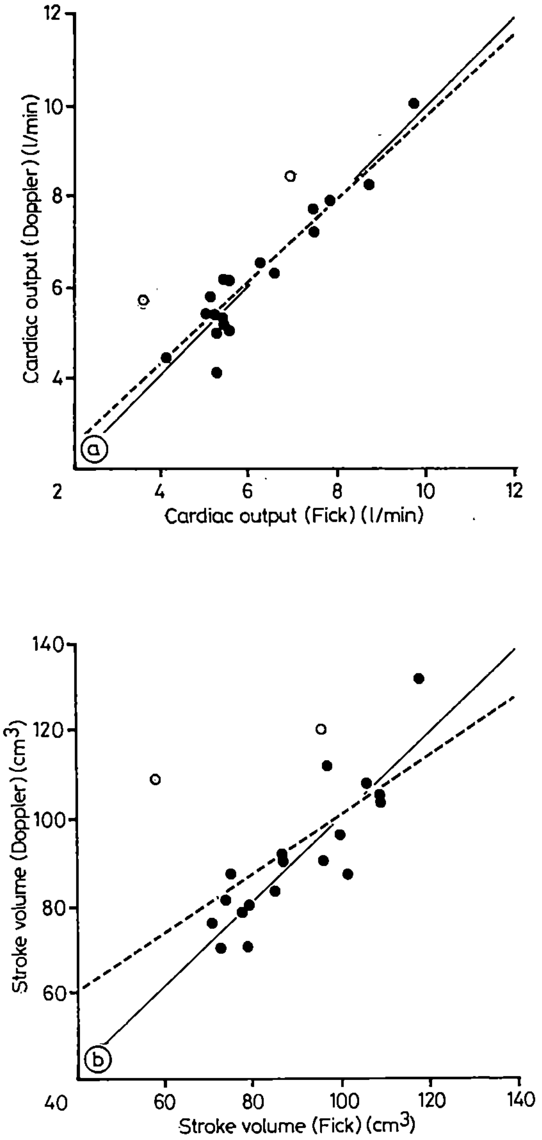

Fig. 4 *Comparison of (a) cardiac output and (b) stroke volume determined by Doppler technique and Fick method. (a) In the whole group (broken line) including two patients (O) with mitral regurgitation (MR), the equation for the linear regression was y=0·90x+0·80, r=0·89, p<0·001, SEE 0·71 l/min. In patients without MR (continuous line) the equation was y=0·97x+0·22, r=0·95, p<0·001, SEE 0·49 l/min. (b) In the whole group (broken line) including two patients (O) with mitral regurgitation (MR), the equation for the linear regression was y=0·70x+30·79, r=0·66, p<0·005. In patients without MR (continuous line) the equation was y=0·95x+4·83, r=0·87, p<0·001.*

CARDIAC CATHETERISATION

The cardiac output by the Fick method ranged from 3·8 to 9·8 l/min (6·1 (1·5) l/min). The highest value was found in one normal subject (case 2), who also had the highest cardiac output by Doppler echocardiography. The lowest value was found in one patient with coronary artery disease (case 16), whose cardiac index by the Fick method was <2·5 l/m^2 per min. The stroke volume varied between 58 and 118 cm^3 (89 (16) cm^3). The highest value was in one normal subject (case 13), who also had the highest stroke volume by Doppler echocardiography. The lowest value was in the patient with the lowest cardiac output by the Fick method.

COMPARISON BETWEEN DOPPLER ECHOCARDIOGRAPHY AND CARDIAC CATHETERISATION

There was a highly significant correlation for cardiac output between Doppler echocardiography and the Fick method (r=0·89, p<0·001, Fig 4). In the two patients with mitral regurgitation, however, the Fick results were considerably overestimated by Doppler echocardiography. If these two patients were excluded, an excellent correlation was derived (r=0·95, p<0·001). The cardiac output by the Fick method was not significantly different from that measured by the pulsed mode using the diastolic velocity integral from either position A or B; nevertheless, it was considerably overestimated by the continuous mode and underestimated by the pulsed mode using the velocity integral from position C (Fig. 3).

There was no significant difference between the heart rates during the Doppler and Fick procedures (68 (15) beats/min *vs* 69 (13) beats/min), and the stroke volumes derived from the two measurements could therefore be compared. There was a significant correlation of stroke volume between the two techniques (r=0·66, p<0·005, Fig. 4). In the two patients with mitral regurgitation, however, stroke volume was also overestimated by Doppler echocardiography. If these two cases were excluded, a highly significant correlation was also obtained (r=0·87, p<0·001).

Discussion

Volumetric flow measurements using Doppler echocardiography require (*a*) a correct determination of the cross sectional area, (*b*) a flat velocity profile at this site, and (*c*) a near alignment between the Doppler beam and the flow direction. Theoretically, there are two places in the left ventricular inflow tract where the mitral cross sectional area could be measured. One is at the mitral annulus, the inlet of the mitral valve, and the other is at the mitral valve orifice, the outlet of the mitral valve. Since the mitral annular cross sectional area is difficult to localise on an echocardiogram the annular diameter has been used to calculate the area.[10] Ormiston *et al* showed, however, that changes in a single echocardiographic annular diameter may not predict changes in annular area since both the position and shape of the annulus may change during the cardiac cycle.[11] On the other hand, the mitral orifice area can be determined precisely by planimetry in the cross sectional short axis view. To achieve an optimal measurement, it is mandatory that the maximal orifice area at the valve tips should be recorded. In their study, Fisher *et al* planimetered the mitral orifice area through the middle of the leaflets,[7] but in most other studies[12 13] the mitral orifice area was measured on a trailing to leading edge basis. The latter method has proved to be accurate and reproducible[14] and hence has been used in the study.

Since the mitral orifice area changes considerably during diastole it is necessary to correct for such variations. Theoretically, it would be more accurate to measure area changes over all diastolic frames. This procedure is, however, tedious and time consuming. Moreover, because the mitral valve tips move in and out of the sectional plane during diastole it is practically impossible to obtain all the cross sectional areas throughout the cardiac cycle. Nevertheless, as the normal mitral orifice is elliptical,[8] and its area changes are mainly due to the movement of both leaflets in the anteroposterior direction,[15 16] such changes could be predicted by the variations in the anteroposterior diameter—that is, the variations of the leaflet separation that can be calculated on derived M mode echocardiograms. The mean to maximal opening ratio, as described previously by other workers,[6 17] is a correction factor for the changes in diastolic area. In contrast to their method of dividing the M mode diastolic recording into 0·05 s segments in one cardiac cycle we performed planimetry of the whole separation area over 10 cardiac cycles, which may provide a more accurate mean opening diameter and opening ratio.

The diastolic flow pattern through the mitral valve in sinus rhythm is complex including two acceleration and deceleration phases combined with alterations in cross sectional area. Despite this, experiments on normal mitral valves have shown a fairly flat velocity profile at the mitral annulus and a slightly peaked profile at the valve orifice.[8] The Doppler measurements therefore estimate the mean spatial velocity profile with a reasonable degree of accuracy provided that it is made at the site where the area is determined and in alignment with the flow direction. Duplex Doppler echocardiography has reduced these problems by visualising the sample volume and showing the Doppler angle within the sectional plane. Nevertheless, the angle within the elevational or azimuthal plane still cannot be determined.[17] In such circumstances, we believe that the single Doppler technique using the apical approach and the audio signals is well able to obtain an optimal beam direction for the mitral flow. By moving the Doppler sample from the left ventricle step by step to the left atrium, the amplitude signal from the mitral valve movement can be recorded and used to determine the optimal sample location. The level at which the valve opening is first recorded (position A) is probably the level of the mitral valve tips. This statement may not be true because the mitral valve moves constantly relative to the chest during diastole. We therefore measured the velocity at position B (1 cm above position A). The fact that there was no significant difference in the velocity integral between the two positions indicates that small changes in sample location are unimportant in the measurement of mitral flow. On the other hand, the velocity integral recorded from position C was signficantly smaller than that from either A or B. The reason for this is probably that at this level the sample has reached the mitral annulus whose area is much larger than that of the mitral orifice so that the flow velocity is decreased. These findings agree with previous observations.[18]

The good correlations of cardiac output and stroke volume between pulsed Doppler echocardiography and the Fick method obtained in this study confirm the reliability of the mitral orifice method in determining cardiac output. Although we did not measure cardiac output simultaneously by the two techniques, similar heart rate during the two examinations suggests that there was no important haemodynamic difference between the two procedures. In contrast, cardiac output was significantly overestimated by the continuous mode. This is probably because when a sample volume in the mitral flow canal approaches the left atrium the early diastolic velocity decreases, whereas the late diastolic velocity increases.[18] The continuous mode picks up both the highest early and late diastolic velocities, resulting in an overestimated cardiac output. It seems, therefore, that in the mitral orifice method only the pulsed mode can be used. Our data also show that both the diastolic velocity integral and the maximal mitral orifice area correlated significantly with the stroke volume by Doppler echocardiography; nevertheless, because the values are scattered use of either the mitral echocardiograms[19] or mitral flow characteristics alone is an unreliable method for estimating cardiac output.

There are some limitations to this method. Firstly, mitral valve disease makes the measurement unreliable, as shown by the two patients with mitral regurgitation. Secondly, any congenital heart disease with a shunt below the level of the mitral orifice would produce similar results. Finally, since both area and flow of the mitral orifice are very variable measurement of a number of cardiac cycles is necessary and hence time consuming.

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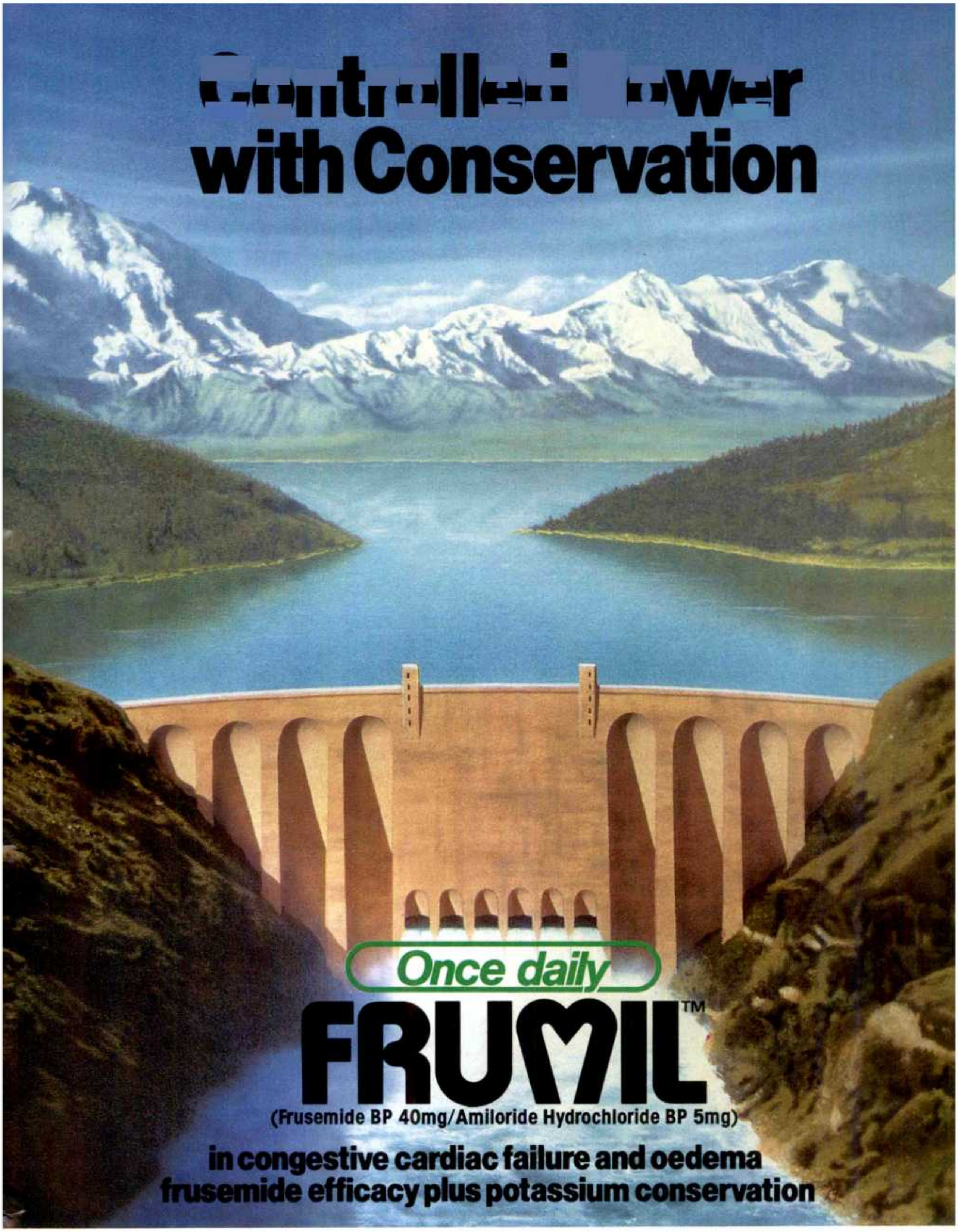
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Non-invasive estimation by cross sectional echocardiography of myocardial damage in cardiomyopathy

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SUMMARY Retrospective and prospective studies of high resolution cross sectional echocardiograms were undertaken in order to establish an ultrasonic method for the non-invasive estimation of degeneration and fibrosis of the endomyocardium in cases of cardiomyopathy. When the echocardiograms of the ventricular wall were compared with the histological specimens intense abnormal echoes were seen at the sites of myocardial degeneration and fibrosis of the ventricular wall. The abnormal echoes classified into five types: types I, II, III-1, III-2, and III-3. Type I and type III-1 echoes were the strongest followed by those of types II and III-2, and then those of type III-3. The intensity of the abnormal echoes was 5–20 decibels stronger than that from intact tissue and was closely related to the consistency and density of the diseased tissue.

These findings strongly suggest that the boundary between degeneration or fibrosis and the intact normal myocardium was the source of the abnormal myocardial echoes and that the extent and the pattern of the distribution of the sites of degeneration and fibrosis in the myocardium were reflected in the echo patterns. Thus the tissue characteristics of the sites of degeneration or fibrosis of the myocardium may be determined non-invasively by measuring the echo intensity.

The degree of pathological change in myocardial tissue in cardiomyopathy varies from a slight increase in fibrous tissue in the myocardium to massive degeneration or a pronounced increase in interstitial fibrous tissue throughout the myocardium. Nevertheless, cardiac function is largely related to the extent of the myocardial damage. The detection of myocardial degeneration or fibrosis and the evaluation of their extent are, therefore, indispensable for the clinical evaluation of patients.

We have used ultrasonic methods for non-invasively evaluating the changes in tissue characteristics of the valves[1-3] and the myocardium in patients with valvar disease[4,5] and myocardial infarction.[6] The present study was undertaken to assess the applicability of cross sectional echocardiography for detecting myocardial damage in patients with cardiomyopathy. The echocardiographic findings were analysed and compared with those of histological specimens. In addition, studies were undertaken to determine the characteristics of the abnormal echoes of the myocardium by sensitivity graded paired echocardiography.[7,8]

Patients and methods

Twelve patients with hypertrophic obstructive cardiomyopathy, 12 with hypertrophic non-obstructive cardiomyopathy, eight with dilated (congestive) cardiomyopathy, and six with endocardial fibroelastosis, which is one of the allied diseases of cardiomyopathy,[9] were included in this study. In all cases, the diagnosis was established on the basis of clinical investigations.

The specimens for histological examination were

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obtained from the left ventricular wall at necropsy in six cases, by surgical excision in two, and at biopsy in three and stained by Masson's trichrome stain.

ECHOCARDIOGRAPHY

The cross sectional echocardiograms were obtained by a sector scan along the long axis of the left ventricle at the fourth or fifth intercostal space. With a scan along the short axis of the ventricle, the ultrasonic beam frequently hit the hypertrophied ventricular wall obliquely. The image thus obtained was inadequate for measuring the echo intensity because of attenuation of the ultrasound due to the increased length of the pathway through the myocardium.

Echocardiography was carried out with the patient in the supine position using the proximity immersion method[10] in synchronisation with cardiac pulsation within three months of the histological examination. A linear amplifier was used as a receiving amplifier for exact measurement of the echo intensity. The 3·5 MHz transducer used in this study had a concave disc with a diameter of 30 mm and a radius of curvature of 100 mm. The ultrasonic beam was focused at a distance of 90 to 100 mm from the transducer. The width of the beam in the vicinity of the focus was less than 1·0 to 1·5 mm. In a sector scan, the beam was focused on the posterior wall of the left ventricle.

Attenuation of the intensity of the ultrasound during propagation through the heart was compensated for by a sensitivity time control circuit. This circuit was adjusted so that the intensity of the chest wall echo became almost the same as that of the echoes outside the posterior ventricular wall (pleuropericardial echoes). For the evaluation of the echo pattern of the left ventricular wall, the gain setting of the receiving amplifier was set at an optimum level of about 25 to 30 dB higher than the standard level, at which no noise echoes occur in the left ventricular area.

In sensitivity graded paired echocardiography,[7 8] six to eight images obtained by changing the gain setting of the receiving amplifier by 5 to 6 dB from the standard gain level were used for measuring the echo intensity. The intensity of the abnormal echoes in the endocardium and myocardium was measured in decibels by determining the difference between the gain level of the standard echo and the gain level at which the abnormal echoes emerged. In this way, the intensity of the abnormal echoes could be measured by interpolation with an accuracy of about 3 dB.

The gain level at which pleuropericardial echoes emerged is used as a standard (0 dB) because (*a*) the posterior aspect of the pericardium is close to the left ventricular wall, (*b*) the pleuropericardial echoes are stronger than those of other cardiac structures, (*c*) the pleuropericardial echoes can be recorded in all subjects examined, and (*d*) in a sector scan along the long axis of the heart at the parasternal border in the fourth or fifth intercostal space, the pericardium is concave towards the chest wall. Usually the direction of the ultrasonic beam is almost perpendicular to the ventricular wall and pericardium except in cases of pericardial effusion.

The range of intensity of abnormal echoes was measured as the difference between the gain level of the strongest abnormal echoes and that of the weakest ones on the same plane of scan.

The echocardiographic findings were compared with the histological findings of specimens taken from the site that was closest to the area of the ultrasound image.

Results

LEFT VENTRICULAR WALL ECHOES

On the echocardiograms obtained at the optimum gain level, abnormal echoes that were absent in normal subjects were seen in the area of the left ventricular wall in patients with cardiomyopathy. Table 1 summarises the echo findings in all patients, which are classified according to the type of echo.

The abnormal echoes were classified into three types (Fig. 1).

Type I—Very strong wide homogeneous (band shape) echoes were present at the endocardium and subjacent myocardium (Fig. 1a).

Type II—Strong irregular echoes were localised in the inner half of the myocardium subjacent to the endocardium (Fig. 1b).

Type III—Freckle-like echoes were distributed evenly or unevenly throughout the myocardium (Fig. 1c). The type III echoes were further classified into three subtypes (Fig. 2): (*a*) inhomogeneous large freckle-like echoes (Fig. 2a), (*b*) scattered homogeneous, medium sized, freckle-like echoes which occasionally appear in a reticular pattern (Fig. 2b), and (*c*) micronodular or inhomogeneous powdery echoes (Fig. 2c). Echoes similar to the powdery echoes of type III-3 are frequently seen in normal hearts. Occasionally it is difficult to differentiate echoes of type III-3 from powdery echoes in normal hearts on the basis of their echo characteristics.

CORRELATION BETWEEN ECHO TYPES AND HISTOLOGICAL FINDINGS

Patients with similar echocardiographic characteristics had similar histological findings. In patients with type II echoes pronounced degeneration and an increase in fibrous tissue in the endocardium and diffuse or focal fibrosis in the inner half of the left ventricular wall were seen.

The type II echo was found to be intermediate be-

Table 1 *Echocardiographic findings in relation to clinical diagnosis*

Case	*Age (yr)*	*Sex*	*Diagnosis*	*Echo type*	*Echo intensity* (dB)*	*Echo intensity range† (dB)*	*Addendum*
1	46	F	COCM	III-1	10	5	
2	20	M	COCM	I	5	5	
3	23	F	COCM	II	20	0	
4	22	F	COCM	III-2	18	10	
5	32	F	COCM	III-2	20	5	Postpartum (necropsy)
6	35	M	COCM	III-3	25	5	
7	40	M	COCM	I	10	5	(Biopsy)
8	27	M	COCM	III-1	15	10	(Necropsy)
9	1	F	EFE	I	5	3	
10	4	M	EFE	II	15	0	
11	5	M	EFE	II	18	6	
12	6	F	EFE	I	15	5	(Necropsy)
13	3	F	EFE	III-2	20	5	
14	4	M	EFE	II	15	10	
15	50	M	HCM	III-3	24	5	
16	44	M	HCM	II	15	15	(Necropsy)
17	72	M	HCM	III-1	6	10	Nephrosis (necropsy)
18	32	F	HCM	III-3	30	0	
19	20	F	HCM	II	24	5	
20	26	M	HCM	III-2	25	15	
21	37	M	HCM	III-3	25	0	(Biopsy)
22	21	F	HCM	III-2	12	5	
23	25	M	HCM	III-1	10	15	
24	41	F	HCM	III-1	5	20	Nephrosis
25	23	M	HCM	II	15	10	
26	23	M	HCM	III-3	30	5	(Biopsy)
27	16	M	HOCM	II	15	10	Asymmetric (−), septal hypertrophy
28	31	M	HOCM	II	24	5	Asymmetric (+), septal hypertrophy
29	39	M	HOCM	III-3	30	0	Asymmetric (−), apical hypertrophy
30	48	M	HOCM	III-3	25	5	Asymmetric (−), diffuse hypertrophy
31	16	M	HOCM	III-2	20	15	Asymmetric (+), septal hypertrophy (biopsy)
32	40	M	HOCM	II	20	10	Asymmetric (+), septal hypertrophy
33	35	M	HOCM	III-2	25	5	Asymmetric (+), septal hypertrophy
34	37	F	HOCM	III-2	20	5	Asymmetric (−), diffuse hypertrophy (necropsy)
35	46	F	HOCM	III-2	15	15	Asymmetric (+), diffuse hypertrophy
36	49	M	HOCM	II	15	15	Asymmetric (+), apical hypertrophy
37	39	M	HOCM	II	20	5	Asymmetric (+), septal hypertrophy (biopsy)
38	13	M	HOCM	II	24	0	Asymmetric (+), septal hypertrophy

*Gain setting of the receiving amplifier when abnormal echoes emerge.

†Difference between the gain level of the strongest abnormal echoes and that of the weakest ones.

COCM, congestive cardiomyopathy; EFE, endocardial fibroelastosis; HCM, hypertrophic non-obstructive cardiomyopathy; HOCM, hypertropic obstructive cardiomyopathy.

tween types I and III as regards echocardiographic and histological findings except for differences in the distribution of fibrous tissue. The results from patients with type II echoes are therefore not given. Only the findings of representative cases with type I and type III echoes are given.

Type I echoes (Fig. 3, case 7)

A strong wide echo was present in the endocardium and subjacent myocardium (Fig. 3a); the margin of the endocardial echo was relatively smooth. Strong homogeneous echoes were detected in the myocardium by a slight increase in the gain setting of the amplifier (Figs. 3b and 3c); the endocardium was relatively smooth, and the sites of pronounced degeneration and an increase in fibrous tissue were evident in the endocardium and the surviving myocardial tissue. Degeneration and fibrosis of the myocardial tissue adjacent to the epicardium were, however, less pronounced than those of the myocardium subjacent to the endocardium (Figs. 3d and 3e).

Type III-1 echoes (Fig. 4, case 17)

Inhomogeneous strong, large, freckle-like echoes were present in the myocardium (Fig. 4). In this patient (case 17), wide strong echoes were evident in the basal to mid portion of the endocardium. Usually the abnormal echoes of type III-1 can be seen as inhomogeneous spotted echoes by decreasing the gain setting of the amplifier (see also Fig. 9). In the endocardium and subjacent myocardium, the thick fibrous tissue can be seen as a band that is stained blue. Focal degeneration and diffuse fibrotic changes were present at the sites where strong inhomogeneous freckle-like echoes were visible (Fig. 4c). At the mid-portion, an increase in striped fibrous tissue could be seen in the myocardium, in particular, adjacent to the endocardium (Fig. 4d). An increase in the lattice pat-

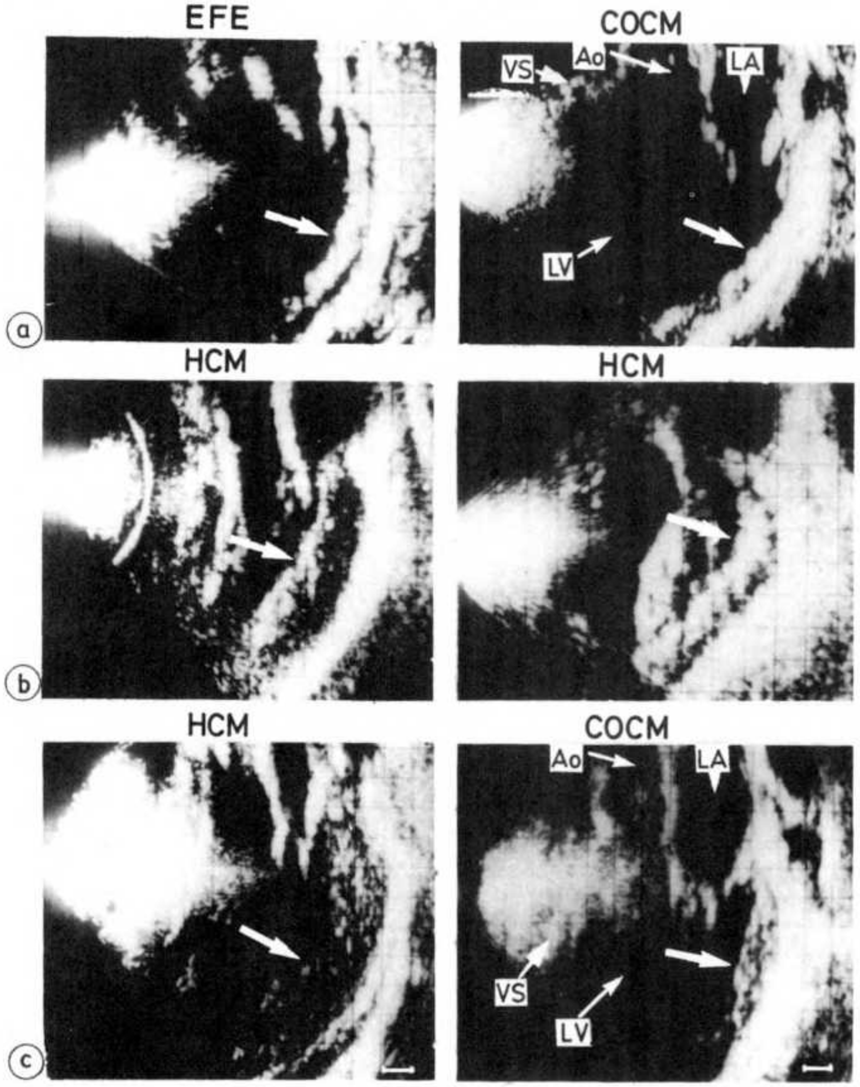

Fig. 1 *Cross sectional echocardiograms showing three types of abnormal echoes (thick white arrows) in the left ventricular free wall in cardiomyopathy (a) type I (case 9 left panel, case 7 right panel); (b) type II (case 25 left panel, case 16 right panel); (c) type III (case 22 left panel, case 5 right panel). The anterior chest wall of the patient is on the left, the right side of the patient at the top, and the left side at the bottom. EFE, endocardial fibroelastosis; COCM, congestive cardiomyopathy; HCM, hypertrophic cardiomyopathy; Ao, aorta; LA, left atrium; LV, left ventricle; VS, ventricular septum. Bar indicates 1 cm.*

tern of the interstitial fibrous tissue throughout the myocardium was also evident. Thus the wide strong (band-shaped) echo in the endocardium was caused by the presence of fibrotic tissue in the endocardium or in the subjacent myocardium (Figs. 3 and 4)

Type III-2 echoes (Fig. 5, case 34)
The echo of the endocardium was rather weak (Fig. 5). Medium sized freckle-like echoes were visible in the myocardium of the left ventricular wall (Figs. 5a and 5b; see also Fig. 10). Histological examination showed a slight increase in fibrous tissue in the endocardium, as evidenced by the scattered small areas that were stained blue throughout the myocardium (Fig. 5c). The areas of degeneration, small to medium in size, were scattered throughout the myocardium. There was an increase in the lattice pattern of fibrous tissue as shown in Fig. 6.

These results suggest that strong freckle-like echoes of uneven distribution occur as the result of focal degeneration or a diffuse increase in fibrous tissue in the myocardium and that the medium sized echoes occur as the result of an increase in the lattice pattern of interstitial fibrous tissue.

Type III-3 echoes (Fig. 7, case 26)
The left ventricular wall and the septum were thicker than normal. Despite a slight increase in the intensity of the endocardial echo, there were powdery echoes in the left ventricular wall (Fig. 7a). When the gain set-

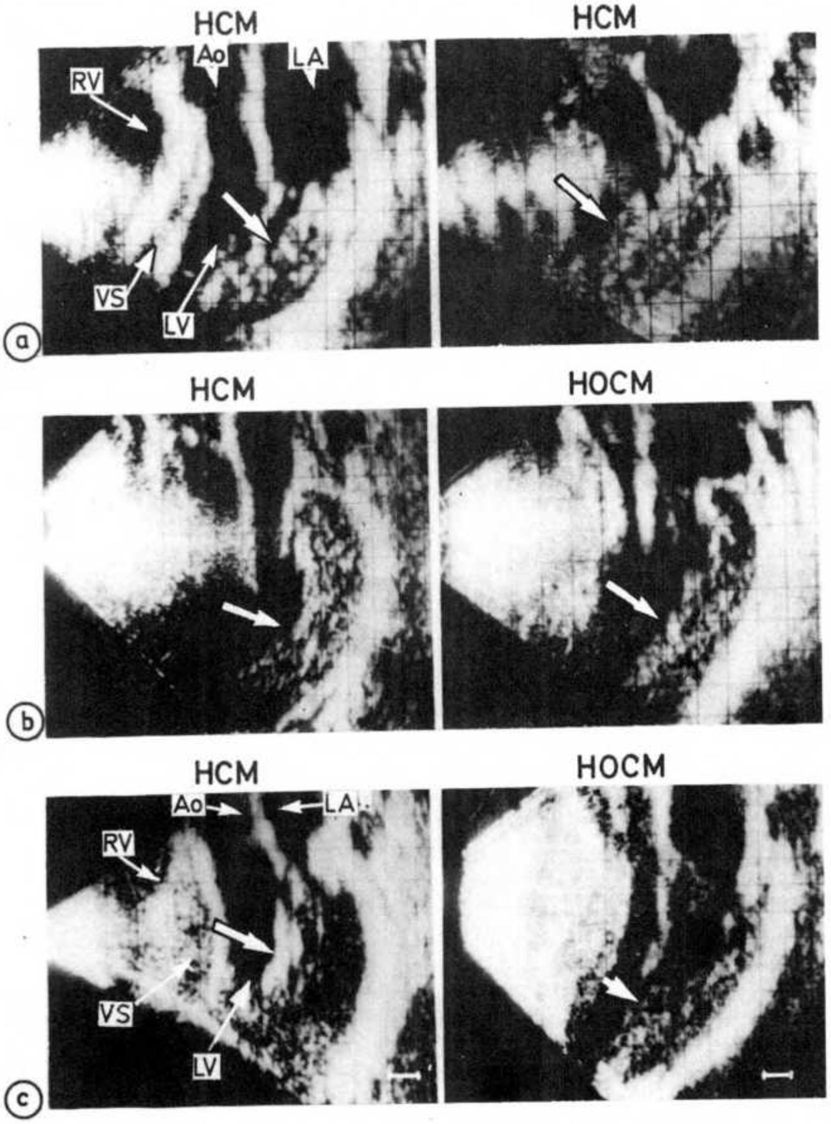

Fig. 2 *Cross sectional echocardiograms showing three subtypes of type III echo. Thick white arrows indicate abnormal echoes. (a) type III-1, large freckle-like echo (case 24 left panel, case 23 right panel); (b) type III-2, medium sized freckle-like echo (case 22 left panel, case 34 right panel); (c) type III-3 micronodular or powdery echo (case 26 left panel, case 30 right panel). Abbreviations as in Fig. 1. HOCM, hypertrophic obstructive cardiomyopathy.*

ting of the receiving amplifier was increased, the echoes became poorly defined or scattered (see Fig. 11 and Fig. 2c, left panel). A slight increase in the fibrous tissue in the endocardium and subjacent myocardium and a slight amount of degeneration of the myocardial fibre were evident (Fig. 7b). The myocardium seemed to be almost intact (Fig. 7c).

INTENSITY OF ABNORMAL ECHOES IN LEFT VENTRICULAR WALL

Tables 1 and 2 summarise the echo intensity and the range of intensity measured by sensitivity graded paired echocardiography.

Table 2 *Range of echo intensity of cardiac tissue*

Tissue	*Intensity (dB)*
Pericardium	0 (standard)
Normal echoes	
Epicardium	10–15
Endocardium	20–25
Myocardium	25–30
Valve, chordae tendinae	15–20
Abnormal echoes	
Scar (infarction)	5–10
Type I	5–15
Type II	15–25
Type III-1	5–10
Type III-2	12–25
Type III-3	24–30

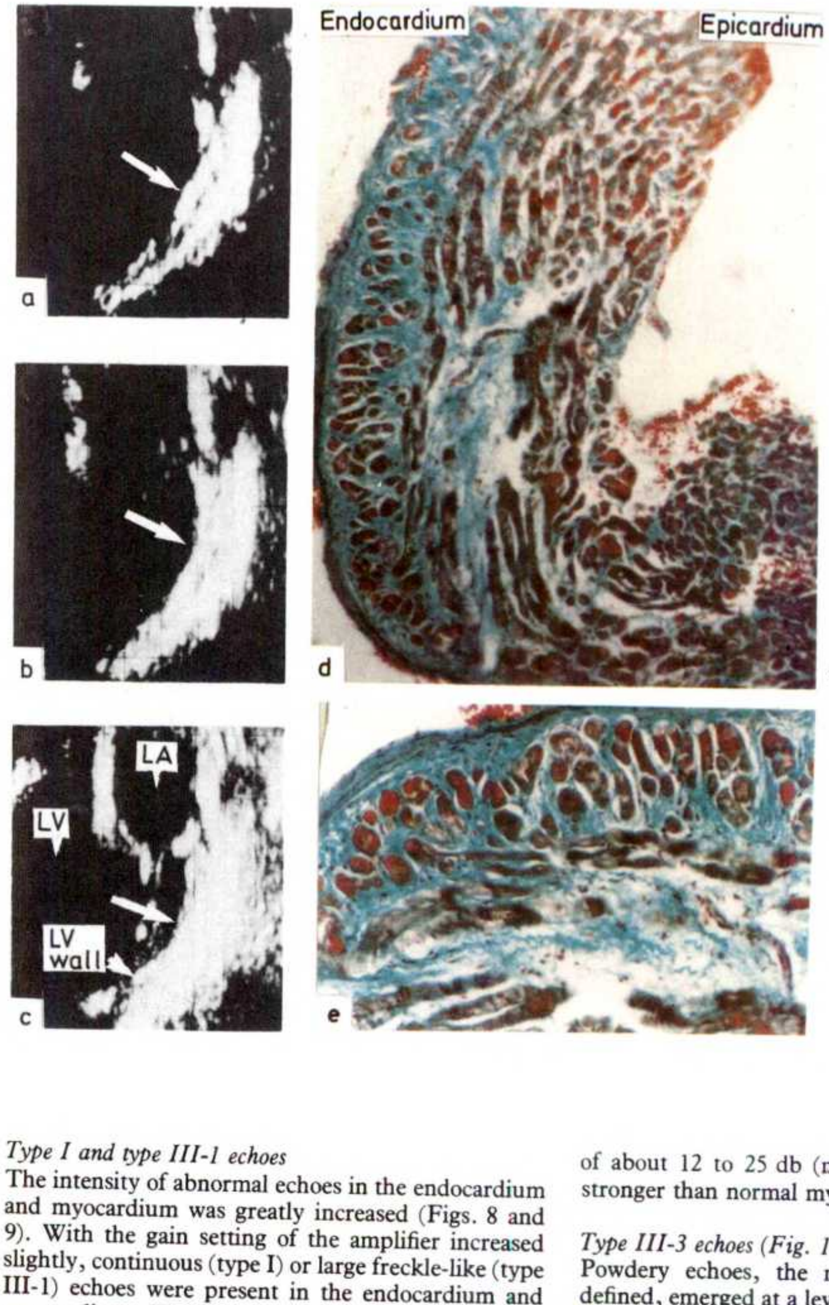

Fig. 3 *Cross sectional echocardiograms showing (a)–(c) type I echo and (d) and (e) histological appearance of biopsy specimen of the endomyocardium of the left ventricular wall from a patient with congestive cardiomyopathy (case 7). The gain setting of receiving amplifier was changed by 5 dB steps: (a) was taken at the lowest level and (b) and (c) at higher levels. Thick white arrows show the areas from which biopsy specimens were taken. (d) and (e) show degeneration of myocardial fibre and an increase in fibrous tissue in the myocardium near the endocardium stained blue.*

Type I and type III-1 echoes

The intensity of abnormal echoes in the endocardium and myocardium was greatly increased (Figs. 8 and 9). With the gain setting of the amplifier increased slightly, continuous (type I) or large freckle-like (type III-1) echoes were present in the endocardium and myocardium. These abnormal echoes emerged at a level of 5–15 dB and were about 10–25 dB stronger than normal endocardial or myocardial echoes.

Type II and type III-2 echoes (Fig. 10)

The medium sized freckle-like echoes were at a level of about 12 to 25 db (more than about 5 to 15 dB stronger than normal myocardial echoes).

Type III-3 echoes (Fig. 11)

Powdery echoes, the margin of which is poorly defined, emerged at a level of about 25 to 30 dB. The intensity of these echoes was within normal range.

Intensity range of abnormal echoes (Table 1)

The types I and III-3 echoes were in the narrow range of intensity (0–5 dB). The types II, III-1, and III-2 echoes were either in a narrow (0–5 dB) or a wide range (10–15 dB).

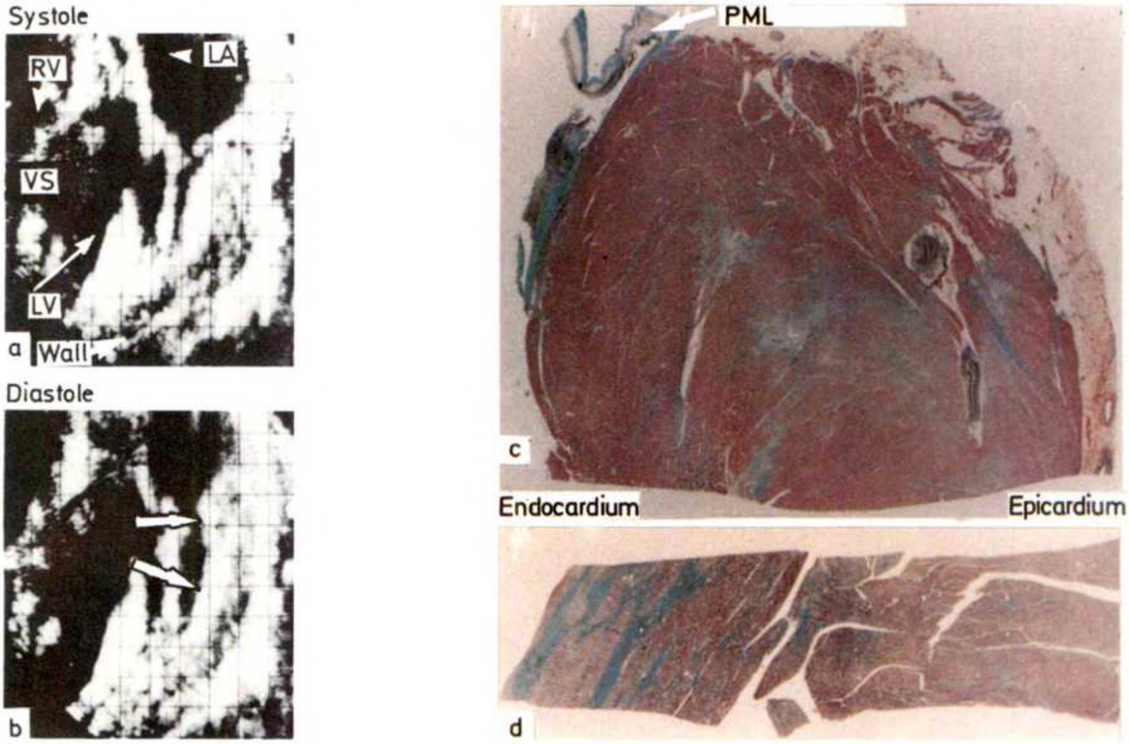

Fig. 4 *Cross sectional echocardiograms showing type III-1 echoes ((a) and (b)) and histological sections of the left ventricular wall ((c) and (d)) (case 17). (c) Sample taken from the basal portion as indicated by the thin white arrow on the echocardiogram (b). (d) Sample taken from the midportion of the left ventricular wall as indicated by the thick white arrow on the echocardiogram (b). Thickening of the endocardium, diffuse myocardial degeneration, and focal fibrosis are found throughout the myocardium of the basal portion. At the midportion of the ventricle band-like and scattered fibrosis throughout the myocardium are stained blue. Abbreviations as in Fig. 1. PML, posterior mitral leaflet.*

Discussion

Thickening of the endocardium in association with subendocardial fibrosis, hypertrophy of cardiac muscle cells, and diffuse or focal interstitial fibrosis of the ventricular wall are the common histopathological findings in cardiomyopathy.[11-13] Irregular arrangements of cardiac muscle cells, degeneration, and pronounced fibrosis of the ventricular septum are frequently seen in hypertrophic cardiomyopathy.[14-16] Accordingly, a non-invasive method of evaluating the changes, as mentioned above, when established will allow a more exact and less laborious estimation of the severity of a cardiomyopathy. For this reason, attempts have been made to apply a well focused ultrasound.

According to the principle of pulse reflection (echocardiography), the occurrence of abnormal echoes as mentioned above strongly suggests that tissue with acoustic characteristics different from those of normal tissues is present and that acoustic boundaries are formed around areas where the abnormal echoes are detected.

To confirm the presence of abnormal tissue the echocardiographic findings were analysed with reference to the histological findings of specimens taken at necropsy or biopsy. As already described, degeneration or fibrosis was present in the endocardium or myocardium at sites where abnormal echoes were detected.

Changes in echo pattern are caused by changes in the acoustic properties of tissue[17 18] and by changes in the size and spatial arrangement of acoustic boundary surfaces and also by machine characteristics.

When the electric circuits, such as a differential circuit and an automatic gain control circuit, are used

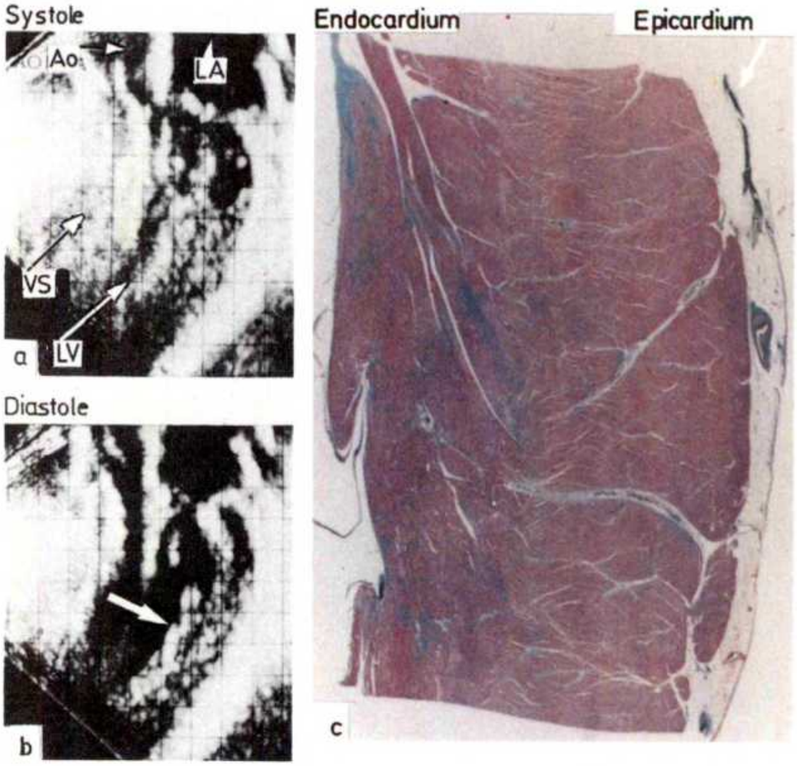

Fig. 5 *Cross sectional echocardiograms showing type III-2 echoes ((a) and (b)) and (c) a section of the left ventricular wall from a patient with hypertrophic obstructive cardiomyopathy (case 34). (c) Sample taken from the midportion of the left ventricular wall (indicated by the thick white arrow in (b)). The sites of fibrosis throughout the entire myocardium are stained blue. A slight thickening and fibrosis of the endocardium and symmetrical hypertrophy of the ventricle are evident. Abbreviations as in Fig. 1.*

to modify the echo signals that are received, so as to make images sharper, this will have a notable effect on the intensity and pattern of echoes. The use of apparatus equipped with modifying circuits like those of a commercial machine will, therefore, be inadequate for the quantitative evaluation of the intensity and echo characteristics. In this study, we paid special attention to the machine's characteristics by installing various devices, such as concave transducers with a large diameter for obtaining sharp directivity and high resolution at the target area, a linear amplifier as the receiver for the exact measurement of differences in intensity of the echo, and an STC circuit for the compensation of ultrasonic attenuation during propagation of the ultrasound. In this study, therefore, the differences in acoustic characteristics of the endomyocardial tissues were clearly distinguished, and the extent and pattern of distribution of degeneration or fibrosis in the myocardium were faithfully reflected by the echo patterns.

Nevertheless, the echo patterns of echocardiograms do not always coincide with the pattern of distribution of fibrous tissue on histological specimens, presumably because: (*a*) the direction of the planes along which the scans were taken does not always exactly coincide with that of the histological sections, (*b*) the resolution of the echocardiograms is weaker than that of light microscopy, and (*c*) histology of the stained specimens shows the distribution of optical dielectric permittivity of the excised tissue, whereas the results obtained by ultrasonic methods show the distribution in vivo of elastic properties.

The propagation of ultrasound through biological tissues is influenced by changes in the three dimensional microscopic structure of the tissue.[19 20] Accordingly, ultrasound may be reflected from abnormal tissue and its surroundings in a different way from normal tissue.[19] Thus changes in the microscopic structure of the tissue within the ultrasonic beam width will be reflected on to the echocardiogram despite the poorer resolution of echocardiography than of light microscopy.

The occurrence of echoes of type I indicates therefore the presence of fibrotic changes in a fairly large area of the endocardium and its surroundings, that of the echoes of type II the presence of fibrotic thickening of the endocardium and focal degeneration or fibrotic changes scattered in the myocardium sub-

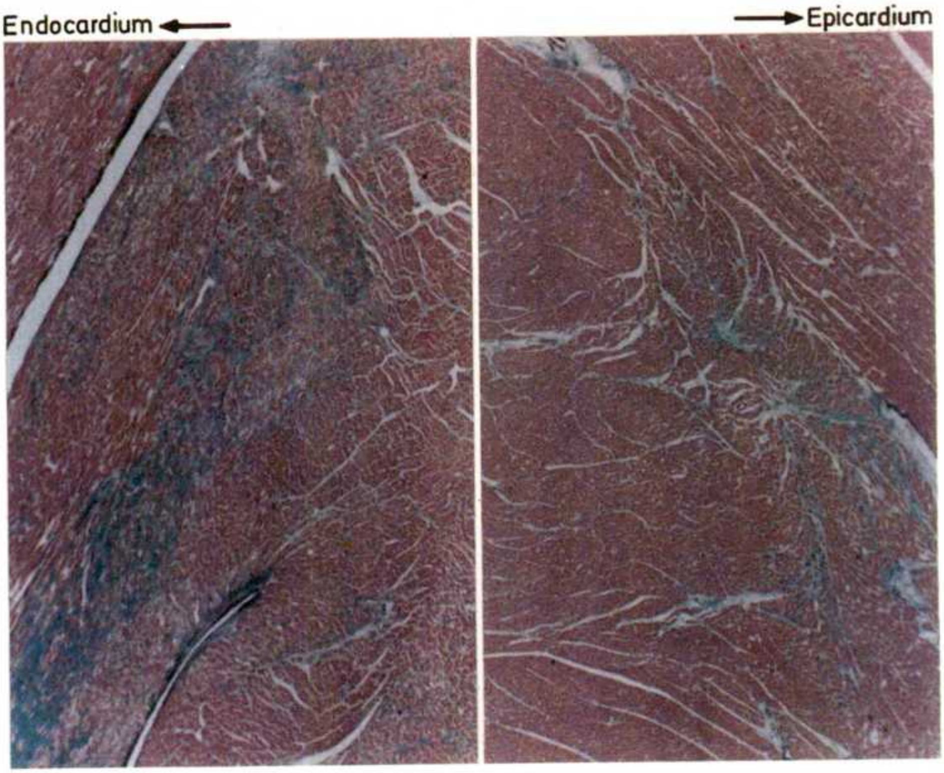

Fig. 6 *Histological appearance of the same section as in Fig. 5 at higher magnification. Sites of fibrosis are stained blue. (×40)*

jacent to the endocardium, and that of the echoes of type III the presence of focal degeneration and diffuse fibrotic changes throughout the myocardium.

Nevertheless, in one patient (case 8) with type III-1 echoes, intertrabecular microthrombi in association with diffuse fibrotic tissue were found at the sites where strong inhomogeneous freckle-like echoes were visible (Fig. 12). The data from this patient suggested that not only scattered focal degeneration and diffuse fibrosis but also organised microthrombi within the dilated trabecular space would give rise to strong large freckle-like echoes in the myocardium.

On the other hand, in sensitivity graded paired echocardiography the types I and III-1 echoes were strongest, followed by types II and III-2 echoes and type III-3 echoes. Abnormal echoes reflected from the site of fibrotic tissue in the endocardium and myocardium of the left ventricle are about 5–20 dB stronger than those from normal tissue (Table 2).

As shown in Table 1, the intensity of types II and III-2 echoes ranged from 15 dB (strong echoes) to 25 dB (weak echoes) in contrast to the narrow intensity range of type I and III-3 echoes. The type II, III-1, and III-2 echoes could be classified into those with a wide range and those with a narrow range of intensity. The occurrence of echoes with a wide range indicated that abnormal echoes increased in number in proportion to the increase in the gain setting of the receiving amplifier and that the echoes with various levels of intensity (from about 10 dB–20 dB) could be found in the same patient (case 23, Fig. 9). The occurrence of echoes within a narrow range of inten-

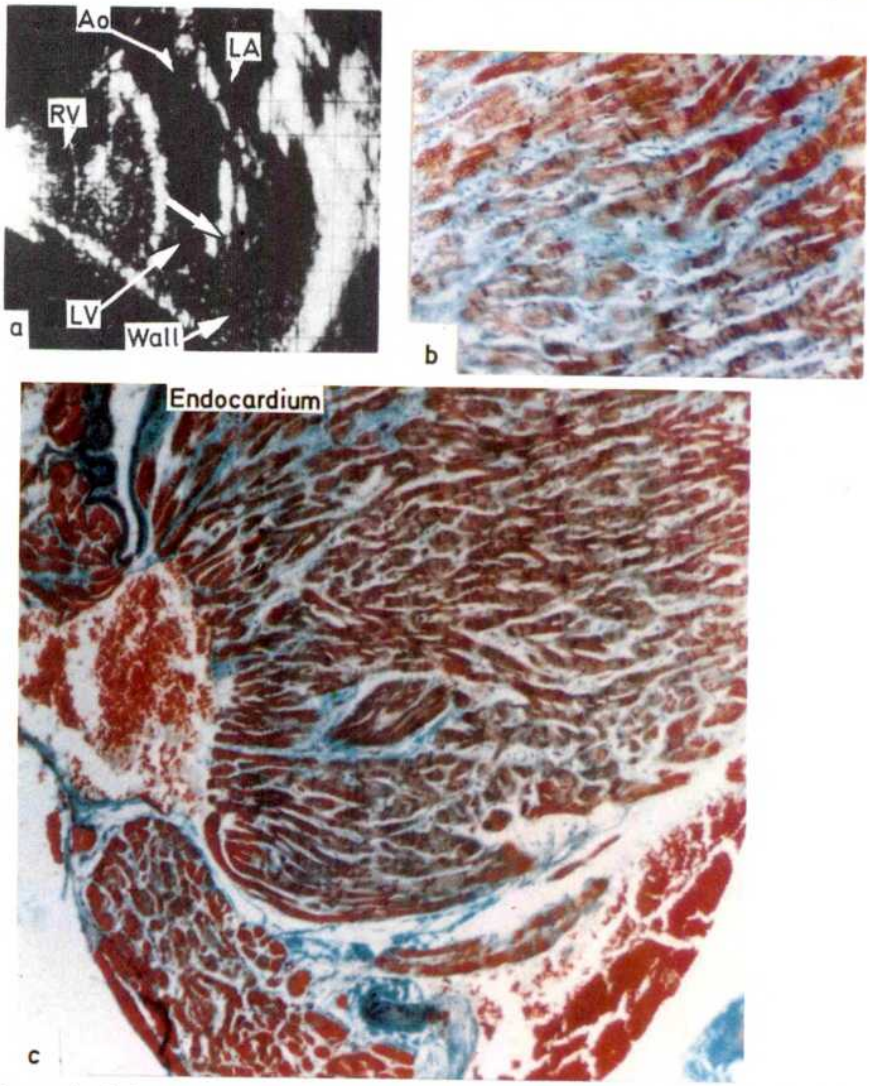

Fig. 7 *(a) Cross sectional echocardiograms showing type III-3 echoes and (b and c) a histological section of a biopsy specimen taken from a patient with hypertrophic cardiomyopathy (case 26), from the site shown by the thick white arrow in (a). (b) Shows the same specimen at a higher magnification. A slight increase in fibrous tissue and degeneration are seen; only a few muscle fibres are affected by degenerative changes.*

sity indicated that almost all abnormal echoes in the myocardium emerged with a slight increase in the gain setting of the amplifier and that the intensity level of abnormal echoes was within a certain gain level (Fig. 10). The area of strong echoes (5–10 dB) corresponded to the area of massive degeneration or pronounced increase in fibrous tissue (Fig. 4a). The area of weak echoes (15–20 dB) corresponded to the site of degeneration or a slight increase in fibrous tissue (Fig. 5b).

The echo intensity depends on the difference in acoustic impedance with a pulsed ultrasonic beam passing from one tissue to the next and on the size and configuration of the boundary surface. The charac-

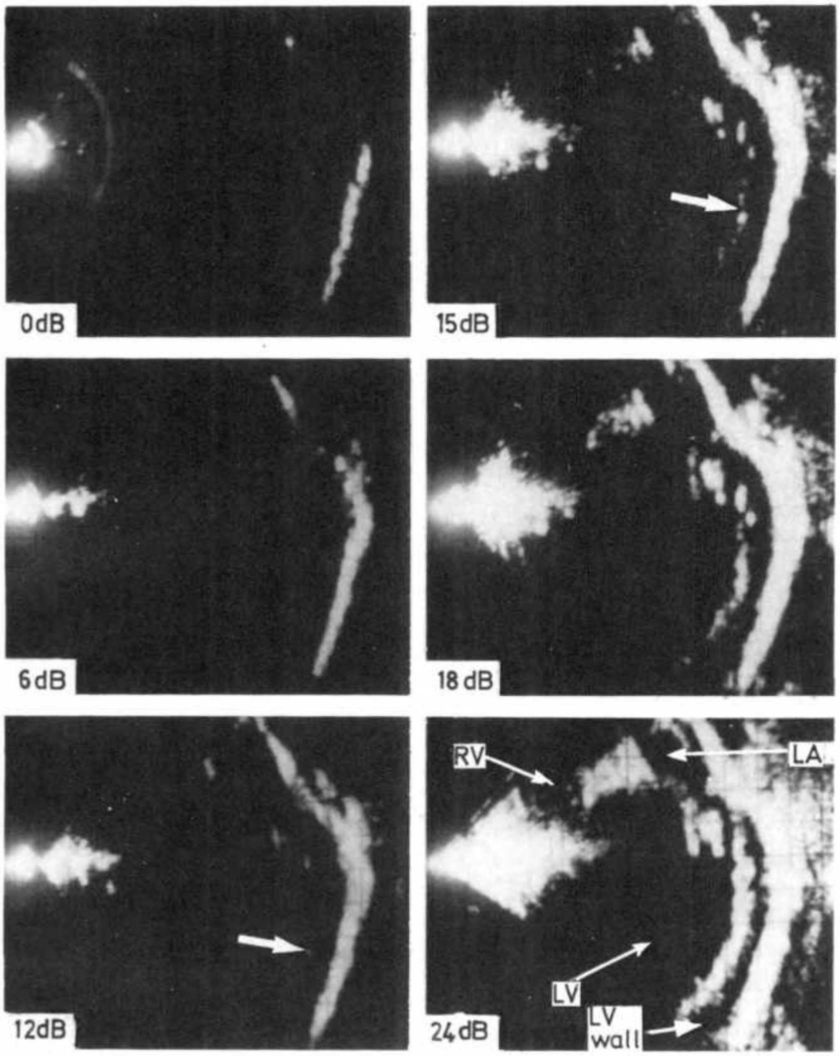

Fig. 8 *Sensitivity graded paired echocardiograms of a patient with endocardial fibroelastosis (case 9). The gain setting of the receiving amplifier was increased in 6 dB steps. Intensified abnormal endocardial echoes emerge at a level of 12 dB (thick white arrows).*

teristic acoustic impedance (z) of a medium is defined by the equation:

$$z = \sqrt{k \cdot \rho}$$

The magnitude of ultrasonic reflection, as shown by reflection coefficient (r), is related to the density and elasticity of the tissues

$$r = \frac{z_2 - z_1}{z_2 + z_1}$$

where k is the bulk modulus of elasticity, ρ the density of the medium, and z_1 and z_2 respectively the characteristic acoustic impedance of the tissue on both sides of the acoustic boundary.

When the structure of the myocardium is affected by destructive changes at a microscopic level, as in tissue degeneration, the boundaries between myocardial fibres within the myocardium may disappear. Then the heterogeneous acoustical medium of the myocardial tissue may become almost homogeneous. Elasticity or stiffness of the diseased tissue becomes different from that of normal tissue when degeneration or fibrotic change occurs in the myocardium. Thus a change in acoustic characteristics and density of the myocardial tissue occurs in association with the destruction of the microscopic structure of the myocardium.[17 18 21]

Furthermore, an increase in the consistency or

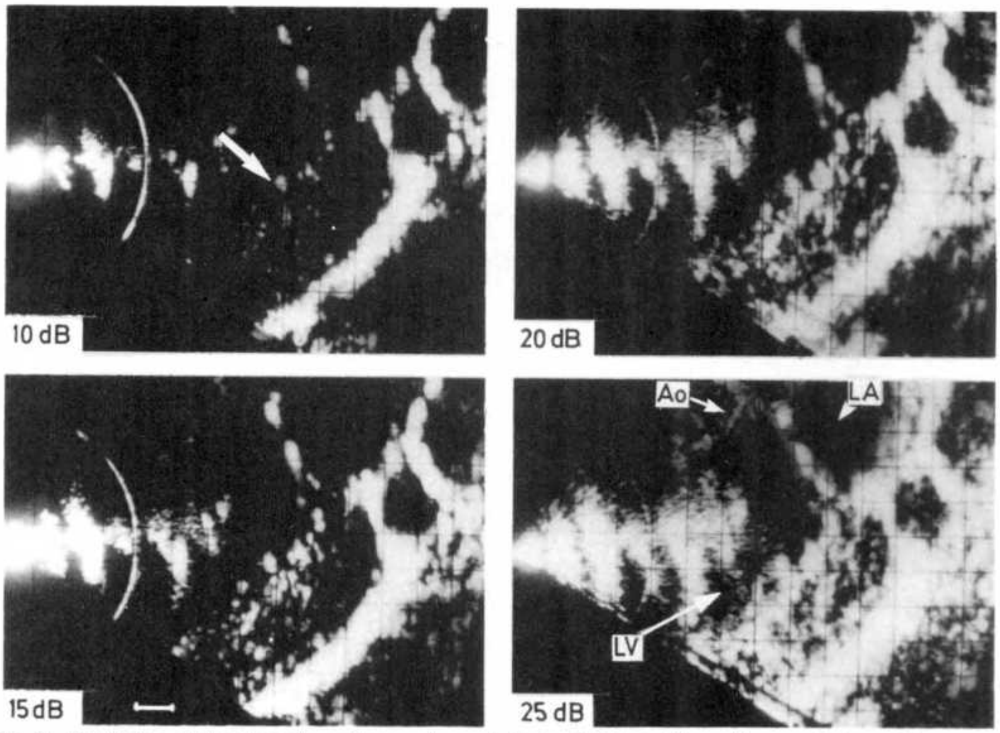

Fig. 9 *Sensitivity graded paired echocardiograms from a patient with hypertrophic cardiomyopathy (case 23). Inhomogeneous large freckle-like echoes (type III-1) in the myocardium emerge at a level of 10 dB (thick white arrow). Echoes at various levels of intensity are detected by increasing the gain setting of the amplifier. Abnormal echoes are seen in a wide range of intensity (15 dB).*

density of the site of degeneration or fibrosis might be correlated with the collagen content of the tissue, as exemplified by the scar of myocardial infarction.[18,21,22] An increase in collagen content causes also an increase in the intensity of the echoes[22-24] that are reflected from the interface between the site of degeneration or fibrosis and normal tissue.

Thus the boundary between the normal myocardium and the area of degeneration or of fibrosis probably serves as a source of echoes, and a change in the intensity of echoes in the left ventricular wall and the intensity of the abnormal echoes are closely related to the consistency and density of the degenerated or fibrotic tissue.[4,6]

Thus the types II and III-2 echoes include echoes from hard or tight fibrous tissue and from soft or loose fibrous tissue. The echoes with a wide intensity range are from fibrous tissue of differing consistency. The abnormal echoes with a narrow range of intensity are from the uniformly diseased area with a similar consistency.

The problem relating to scattering and interference among echoes within biological tissues remains to be solved. Nevertheless, the large strong echoes indicate the presence of tight or massive fibrous tissue and the moderate or small weak echoes that of loose or patchy fibrous tissue in the myocardium. The difference in intensity of the echoes thus probably reflects the differences in the consistency or density of the site of degeneration or fibrosis of the myocardium.

When an ultrasonic beam was focused on the septum, echoes similar to those from the left ventricular wall were also found (data not shown). Usually abnormal freckle-like echoes on the septum are present in the early stages of hypertrophic cardiomyopathy or hypertrophic obstructive cardiomyopathy before abnormal echoes are evident in the ventricular free wall. Such findings in patients with cardiomyopathy suggest that the changes in the septum precede those in the free wall.

In conclusion, the endomyocardial damage of the left ventricular wall in cardiomyopathy can be

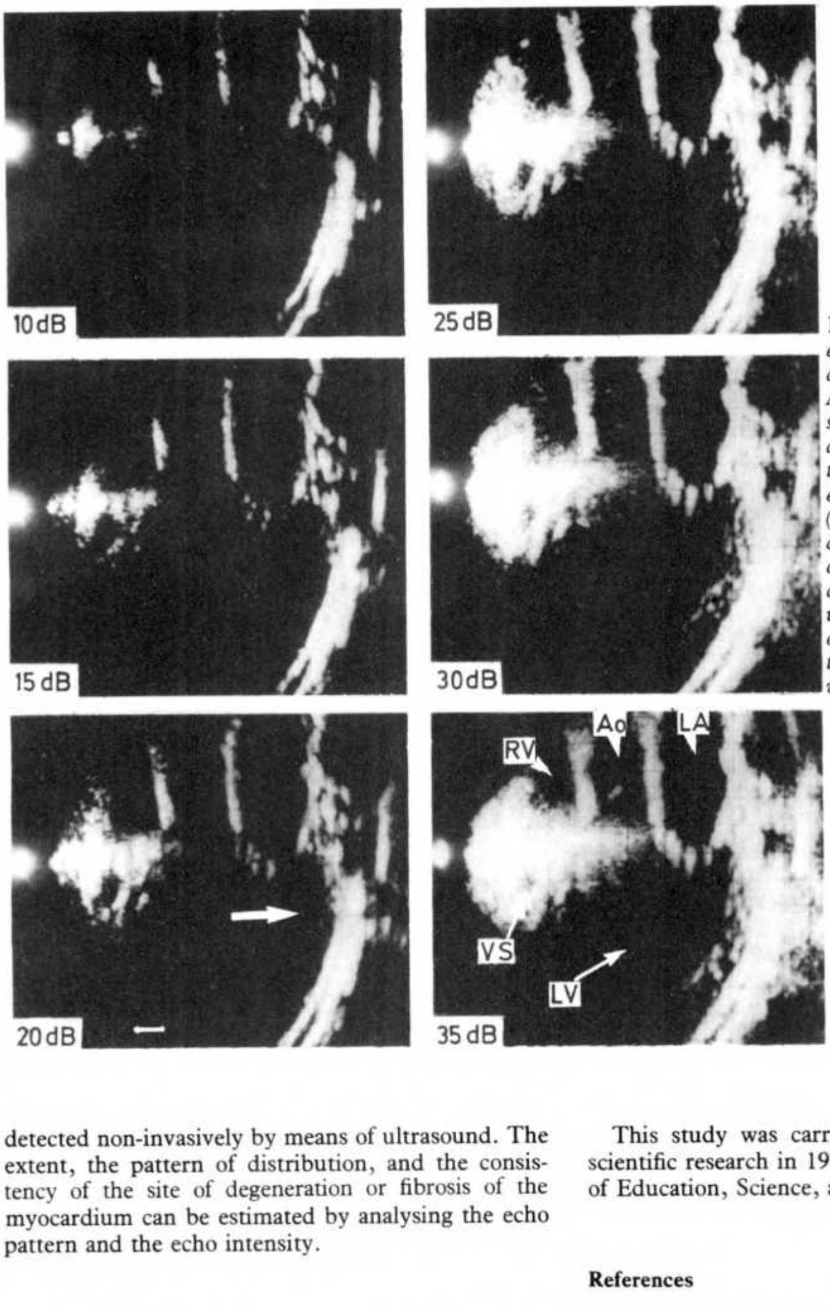

Fig. 10 *Sensitivity graded paired echocardiograms from a patient with congestive cardiomyopathy (case 5). Almost homogeneous and medium sized freckle-like echoes (type III-2) are seen throughout the myocardium of the left ventricular wall. Abnormal echoes emerge at a level of 20 dB (thick white arrow). Almost all the abnormal echoes are already evident at a level of 25 dB. The number of abnormal echoes remained unchanged, even when the gain setting of the amplifier was increased. Thus the intensity of the abnormal echoes was in a narrow range (5 dB).*

detected non-invasively by means of ultrasound. The extent, the pattern of distribution, and the consistency of the site of degeneration or fibrosis of the myocardium can be estimated by analysing the echo pattern and the echo intensity.

We thank Drs Ito, Nagashima and Shinoda, Sendai City Hospital, for allowing us to report on their patients and their biopsy specimens, and Professor F Dunn, Bioacoustics Research Laboratory, University of Illinois, for his advice on acoustical tissue characterisation of heart tissue.

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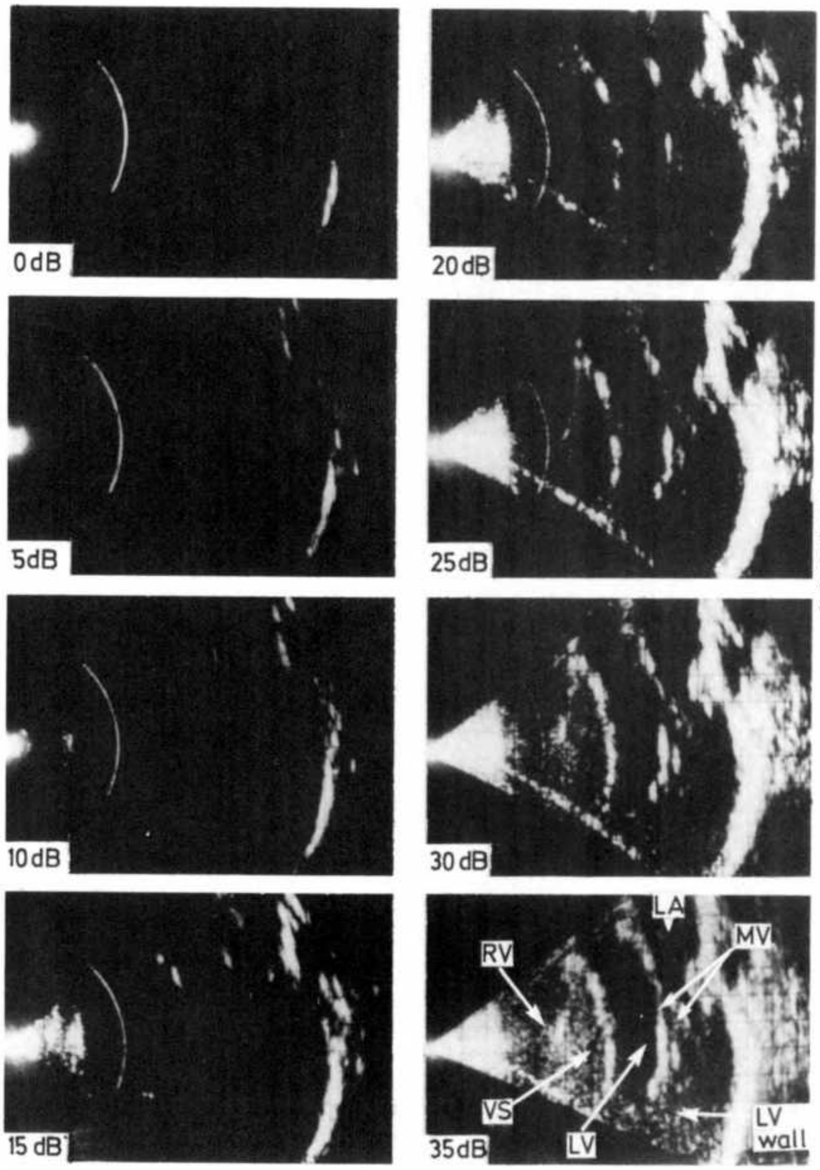

Fig. 11 *Sensitivity graded paired echocardiograms from a patient with hypertrophic cardiomyopathy (case 26). Powdery echoes (type III-3) are seen at a level of 30 dB.*

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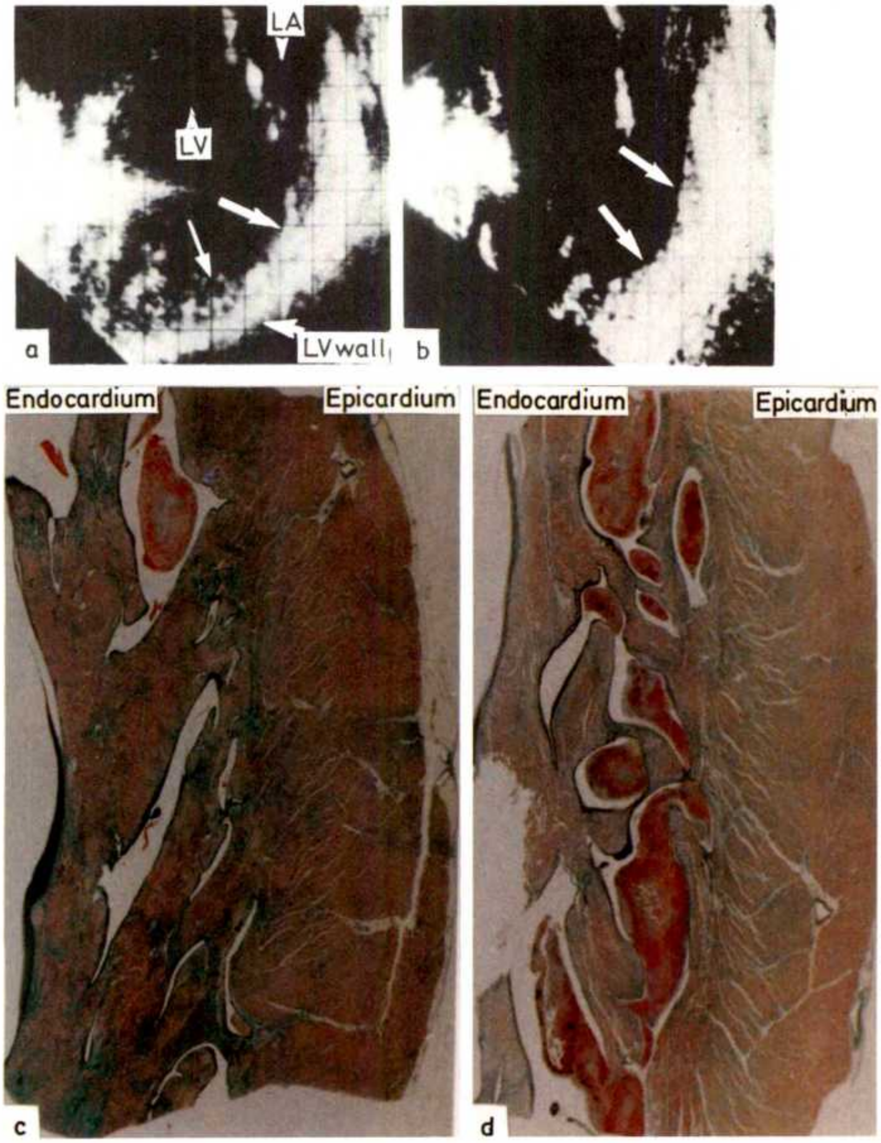

Fig. 12 *Cross sectional echocardiograms in a patient with dilated cardiomyopathy during (a) systole and (b) diastole and ((c) and (d)) a section of the left ventricular free wall (case 8); (c) shows a section at the basal portion of the left ventricular wall, which corresponds to the site shown by the thick white arrow on (a) and (d) shows the apical portion of the left ventricular wall (thin white arrow on (a)). Scattered fibrous tissues (stained blue) are seen throughout the myocardium with numerous microthrombi. The echo pattern of the left ventricular wall is the same as in the type III echo, but there is a large difference in echo pattern between systole and diastole.*

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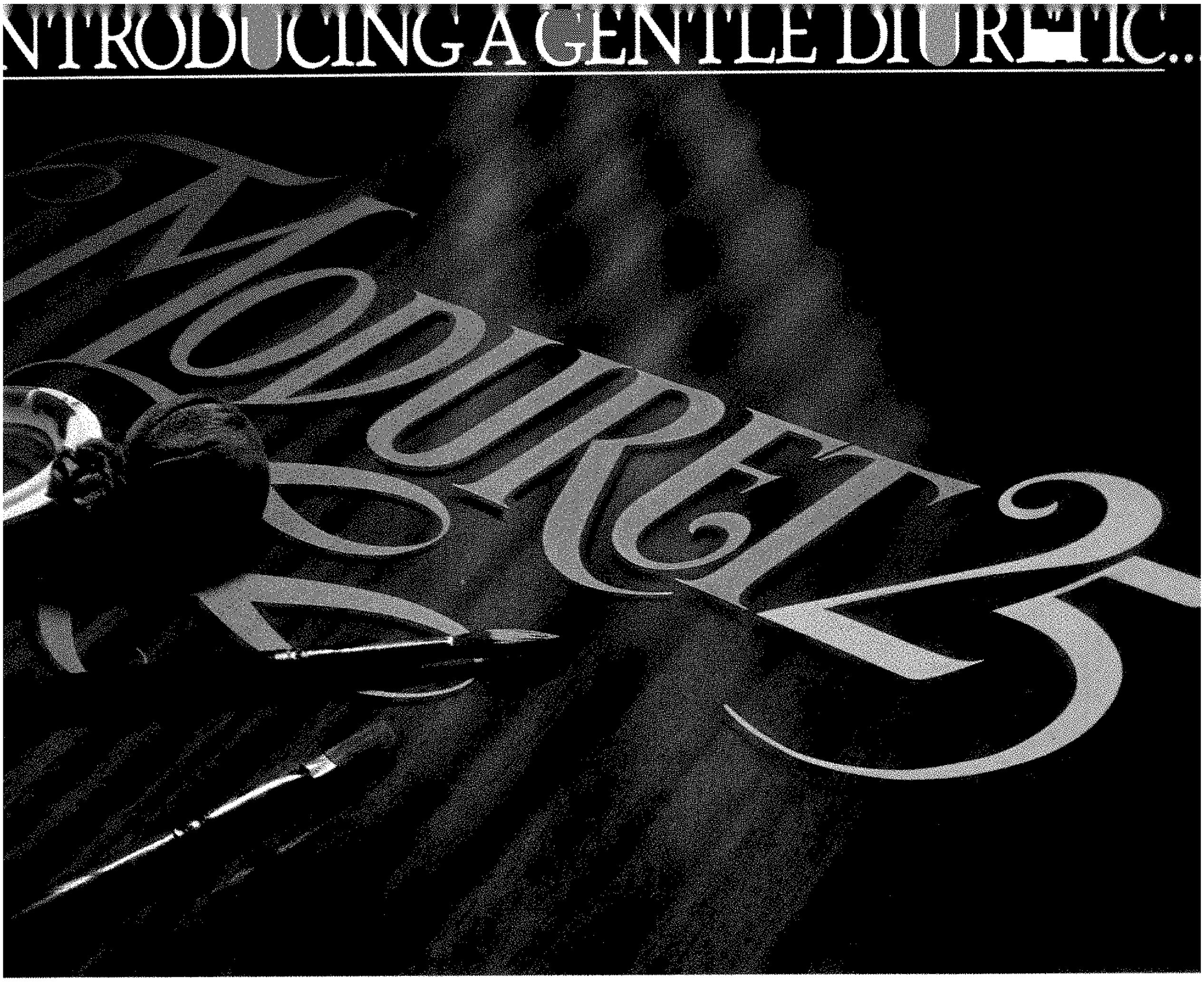

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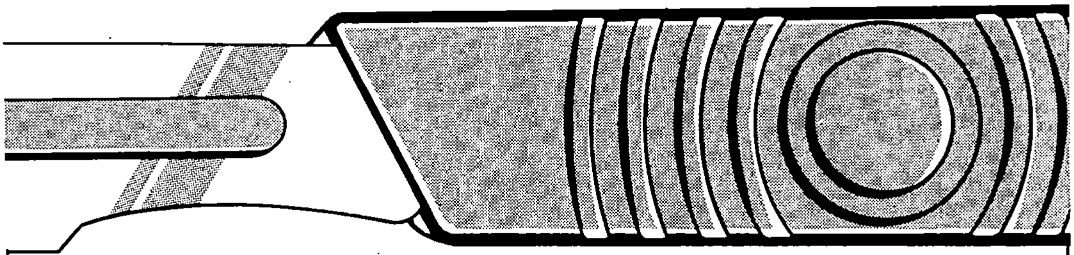

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Somatostatin in the human heart and comparison with guinea pig and rat heart

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*From the Departments of *Medicine and †Histochemistry, Royal Postgraduate Medical School, London*

SUMMARY Somatostatin has been shown to have negative inotropic and chronotopic effects and to restore sinus rhythm in some cases of cardiac arrhythmia. Using acid extracts, regions of human heart were examined by radioimmunoassay to determine their somatostatin content. Mean (SD) concentrations of 4·1 (0·8) pmol/g and 2·9 (0·8) pmol/g were found in atrioventricular node and right atria respectively and were significantly higher than in other heart regions. Using fresh heart tissue from guinea pigs, somatostatin was localised to cardiac nerves by immunocytochemistry. Nerves containing somatostatin were most abundant in the atria, where the concentrations measured by radioimmunoassay were 7·6 (1·0) and 2·6 (0·4) pmol/g for right and left atria respectively.

Somatostatin contained in cardiac nerves may have a physiological role in the cardiac conduction system.

Somatostatin was first isolated as a 14 amino acid peptide from ovine hypothalami[1] and subsequently found also to exist in a 28 amino acid form.[2] It is present in peripheral sympathetic and sensory nerves in mammals.[3] Although there has been no previous report of its presence in mammalian heart, infusion at pharmacological doses in man causes bradycardia and a fall in cardiac output,[4-6] and restores sinus rhythm in cases of paroxysmal supraventricular and junctional tachycardia.[7] We now report that somatostatin is present in the normal human heart, particularly in the right atrium and atrioventricular node, and that in fresh guinea pig heart it can be localised to the neural tissue. Somatostatin endogenous to the heart may therefore play a local role in the conduction system. Nevertheless, a study of the distribution of somatostatin in guinea pig and rat heart showed wide species variation in distribution and molecular form, making it unlikely that either species could serve as a good model for the study of human cardiac somatostatin.

Materials and methods

TISSUE EXTRACTION

Specific regions were dissected from fresh normal postmorten human (n=7), guinea pig (n=5), and rat (n=6) hearts and either frozen rapidly on dry ice and stored at −70 °C until extraction (human) or extracted immediately (guinea pig and rat). In guinea pig and rat, because of the small size of the atrioventricular node a small region of septum containing the node was extracted whole. In the rat, left and right atria were extracted together. Somatostatin was extracted by plunging diced tissue into boiling acetic acid (0·5 mmol) and maintaining it at 100 °C for 10 minutes.

RADIOIMMUNOASSAY

Duplicate 20 μl aliquots of the extract were assayed for somatostatin by a sensitive and specific radioimmunoassay, which has been previously described,[8] using an antibody which cross reacts fully with both the 14 and 28 amino acid forms of somatostatin.

CHARACTERISATION OF MOLECULAR FORMS

Analysis of the molecular forms of the immunoreactive somatostatin in human atrioventricular node was carried out by gel permeation chromatography-using Sephadex G50 gel.

IMMUNOCYTOCHEMISTRY

Whole hearts of adult guinea pigs (n=6, body weight 200–300 g) were removed and promptly fixed in 0·4% benzoquinone[9] made up in phosphate buffered saline (PBS pH 7·2) for three hours at room temperature. After being washed overnight in PBS containing 15% sucrose, the tissues were snap frozen for cryostat blocks. Sections were cut at a thickness of 8 μm and

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Table *Preabsorption test of antisera for immunocytochemistry*

Antisera to	*Antigens**	*Results*
Somatostatin 28 (4–14)	†	Positive
Somatostatin 28 (4–14)	Somatostatin 28 (4–14) (10 nmol/ml)	Negative
Somatostatin 28 (4–14)	Somatostatin 14 (20 nmol/ml)	Positive
Somatostatin 14	†	Negative
Somatostatin 14	Somatostatin 14 (20 nmol/ml)	Negative
Somatostatin 14	Somatostatin 28 (4–14) (10 nmol/ml)	Negative

*nmol antigen/ml of diluted antiserum.
†Without preabsorption with antigen.
Positive, certain nerves were positively immunostained; Negative, no nerves were immunostained.

mounted on poly-L-lysine coated glass slides.[10] A modified indirect immunofluorescence method[11] was carried out.

Antisera to somatostatin 14 and to somatostatin 28 were used; these had been raised in New Zealand white rabbits to somatostatin 14 and 4–14 fragment of somatostatin 28 respectively, which had been conjugated to keyhole limpet haemocyanin by glutaraldehyde.

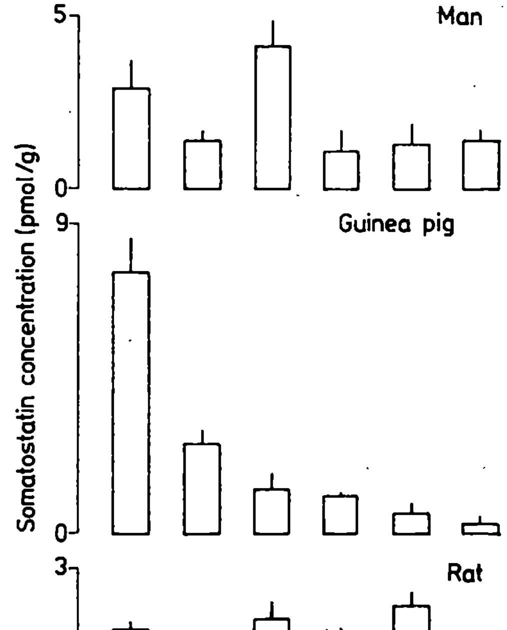

Fig. 1 *Mean (SEM) tissue concentrations of somatostatin in heart regions of man, guinea pig, and rat (pmol/g wet weight). RA, right atrium; LA, left atrium; AV, atrioventricular node; S, septum; RV, right ventricle; LV, left ventricle.*

The controls for immunocytochemistry included preabsorption of the antisera with corresponding antigens, use of normal rabbit serum as the first layer, and omission of the first layer. In addition, the antiserum to somatostatin 14 was preincubated with somatostatin 28 (fragment 4–14) and that to somatostatin 28 (fragment 4–14) with somatostatin 14 in order to check the cross reactivity of the two antisera (Table). The Table gives the characteristics of the antisera.

Results

Figure 1 shows the concentrations of somatostatin in the dissected tissues. In man the highest concentrations of somatostatin were found in the atrioventricular node and right atrium ($p<0\cdot05$ compared with the septum and ventricle wall, Student's paired t test), although there were appreciable concentrations in all regions. In the guinea pig the distribution showed some similarity to that in man, with the highest concentration in the right atrium ($p<0\cdot01$ compared with all other regions). The method of dissection of the atrioventricular node in the guinea pig may have obscured a higher concentration of somatostatin in this region; nevertheless, it was higher than in the ventricular walls ($p<0\cdot01$). In contrast to human and guinea pig heart, the somatostatin concentrations in rat heart regions were generally lower and the distribution was more uniform. Analysis of the molecular form of the immunoreactive somatostatin in the human heart showed it to elute in a single peak, corresponding to synthetic somatostatin 14 (Fig. 2).

Several nerve fibres in the guinea pig heart were found to be immunoreactive to the antiserum against somatostatin 28 (4–14 fragment), and no immunoreactivity was detected using antiserum to somatostatin 14. There were more nerve fibres immunoreactive to somatostatin in the atria than in the ventricles. These immunoreactive nerves were mainly associated with cardiac muscle (Fig. 3) and occasionally with coronary blood vessels (Fig. 4). They were slightly more frequent in the regions of the sinoatrial and the atrioventricular nodes than in other areas. The positive immunostaining could be quenched by somatostatin 28 (4–14 fragment) but not by somatostatin 14 (Table).

Discussion

High somatostatin concentrations are found in human heart tissue in the regions containing specialised pacemaker and conducting cells. Infusions of somatostatin in man cause bradycardia and a fall in cardiac output,[4–6] but the concentrations of somatostatin achieved during the infusions are much higher

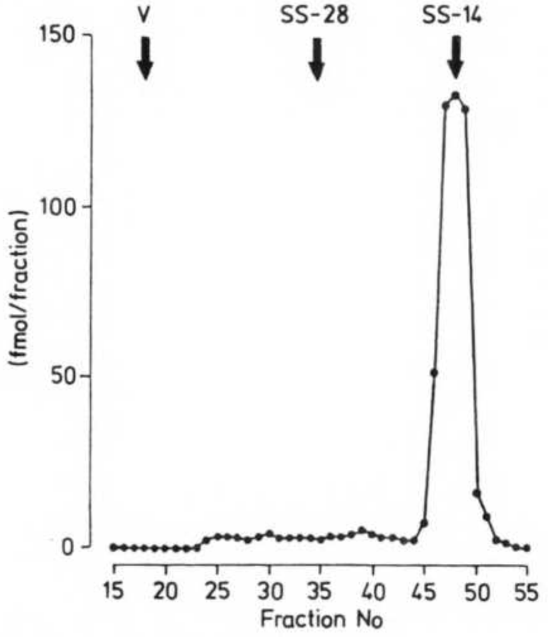

Fig. 2 *Sephadex G50 elution profile of somatostatin immunoreactivity from pooled human atrioventricular node extracts. SS, somatostatin; V, void volume.*

than those found in the peripheral circulation under physiological conditions. It is, therefore, improbable that circulating somatostatin normally affects cardiac function, but endogenous cardiac nerve containing somatostatin could allow an effective concentration to be achieved by local release.

In common with the pattern of tissue distribution between the species, the pharmacological effects of somatostatin on guinea pig but not rat heart[12] are similar to those on human heart. In guinea pigs, somatostatin causes bradycardia and a fall in cardiac output in vivo[13] and exerts a negative inotropic effect on perfused isolated atria.[12]

Other cardiac regulatory peptides—in particular neuropeptide tyrosine—have been found in human cardiac nerves.[14 15] Somatostatin is clearly shown to be contained in nerves in the guinea pig heart, but no fresh human heart was available for examination, and staining of postmortem tissue from peripheral organs with antisera for this peptide is unreliable. It is likely, but not yet proved, therefore, that human cardiac somatostatin is contained in cardiac innervation. Somatostatin has been found in other peripheral tissues in sympathetic and sensory fibres,[3] but the possibility that it may exist in parasympathetic fibres in the heart must be considered, in view of its functional effects and its location in vagal fibres in the heart of the toad.[16] The somatostatin immunoreactive nerves in guinea pig heart are mainly associated with cardiac

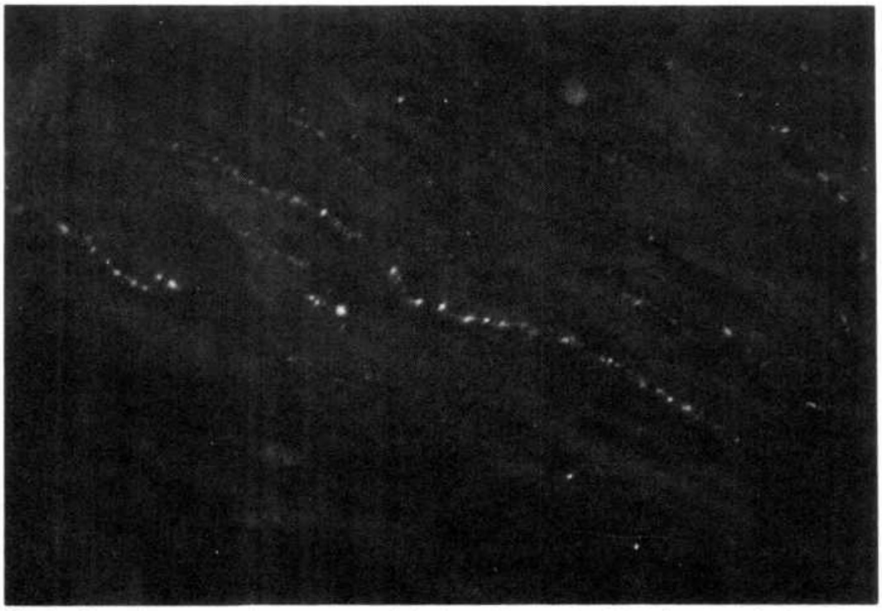

Fig. 3 *Nerves immunoreactive to somatostatin in the cardiac muscle of the left atrium of guinea pig (×450).*

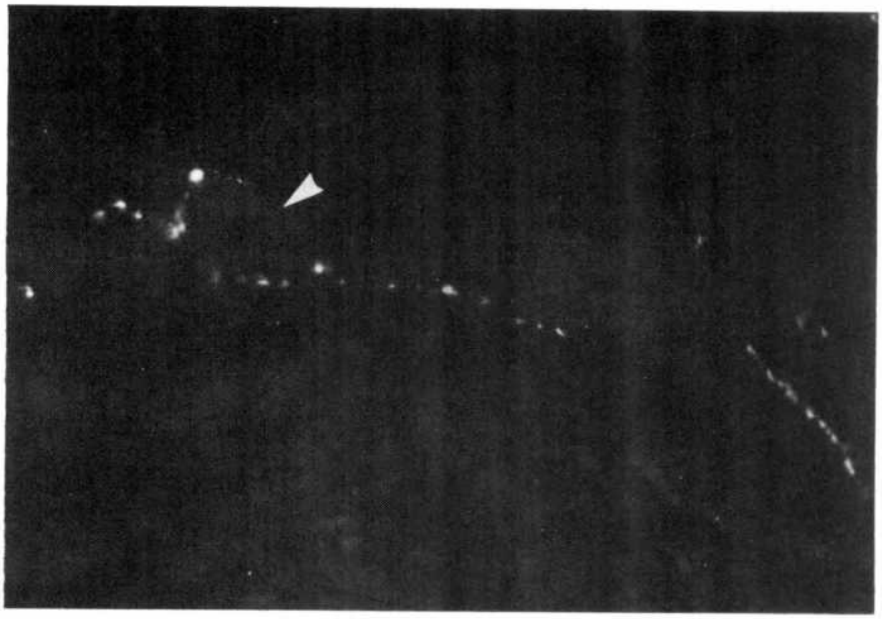

Fig. 4 *Nerves immunoreactive to somatostatin associated with an arteriole (arrow) in the left ventricular myocardium of guinea pig (×400).*

muscle, whereas neuropeptide tyrosine immunoreactive nerves are closely associated with the coronary vasculature in addition to muscle.[17] This implies a possible functional differentiation with cardiac somatostatin acting directly on cardiac tissue rather than on coronary blood flow.

The mode of action of somatostatin at the cellular level is not understood, but there is evidence that it decreases the calcium ion flux into the cell—that is, it acts as a slow channel blocker. The negative inotropic effect of somatostatin on isolated guinea pig atria can be abolished by raising the calcium ion concentration in the perfusing medium.[12] The pacemaker cells of the sinoatrial node and automatic cells in the proximal regions of the atrioventricular node are activated largely by the slow inward current, which may also be observed in other cardiac cells under abnormal conditions. The effect of calcium channel blockers (for example, verapamil) on atrioventricular conduction is of clinical importance in that it provides a mechanism whereby nodal re-entrant supraventricular tachycardia can be abolished and the ventricular response in atrial flutter and fibrillation can be controlled.[18] This may be the mechanism by which intravenously administered somatostatin corrects paroxysmal supraventricular and junctional tachycardia in man.[6] Long and short acting potent analogues of somatostatin are now available and are, therefore, potential new therapeutic agents in cardiac arrhythmias. Further study of somatostatin endogenous to the heart may provide a rational basis for their use.

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Conduction system defects in three perinatal patients with arrhythmia

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SUMMARY The cardiac conduction systems of three patients who died in the perinatal period were studied histologically. Rhythm disturbances were observed in these patients immediately before death. The sinus node was notably hypoplastic without increase in fibrous content in all cases. The atrioventricular node was smaller than expected in all, and the entire atrioventricular conduction axis was small in two cases. This study supports the need for a detailed examination of the cardiac conduction system so as to provide a better understanding of the clinicoanatomical relation in the context of fatal perinatal arrhythmias.

Although the electrophysiological mechanisms of cardiac arrhythmias are well known, very little is known about the structure of the sinus node and atrioventricular conduction system in these circumstances. This is mostly due to the fact that few neonates with conduction disturbances recorded during life have detailed examination of their conduction system after death. Reports of the pathology of the neonatal sinus node are rare. In particular, discrete hypoplasia or underdevelopment of the sinus node is virtually unreported. To the best of our knowledge only one case of hypoplastic sinus node associated with atrial tachycardia has so far been described.[1] Recently, we studied the sinus node and atrioventricular conduction system of three hearts from perinatal patients who had cardiac arrhythmias immediately before death. At presentation, all three patients were thought to have cardiac abnormalities. In this report we consider the clinical significance of the unusual histological findings, especially of the sinus node, in the light of the clinical observations.

Materials and method

The hearts from three perinatal patients with documented conduction disorders were removed at necropsy and fixed in formol saline. Three blocks of tissue were removed from each heart. The first block consisted of the entire junction of the right atrium with the superior caval vein. The orifice of the caval vein was preserved by filling it with a bolus of tissue paper. The second block consisted of the inferior part of the interatrial septum and superior portion of the interventricular septum. The third block comprised the remaining atrioventricular junction. These tissue blocks were processed by the method detailed by Smith *et al*.[2] The tissue paper plug was removed from the first block just before embedding in Fibrowax. Serial sections of 10 μm thickness were cut from each block, and all sections were collected. The first block was sectioned in a plane which cut horizontally across the orifice of the caval vein. The second block was cut in a frontal plane relative to the cardiac septum. The third block was sectioned in planes which profiled the atrioventricular junction. Every twenty fifth section was mounted and stained with a modified Masson's trichrome technique. Further sections were stained where necessary.

CLINICAL DETAILS

Case 1

The mother was admitted for hospital observation because her pregnancy was "large for dates" and showed hydramnios. The fetus was noted to have episodes of supraventricular tachycardia and heart rates up to 300 beats/min. The fetal arrhythmia did

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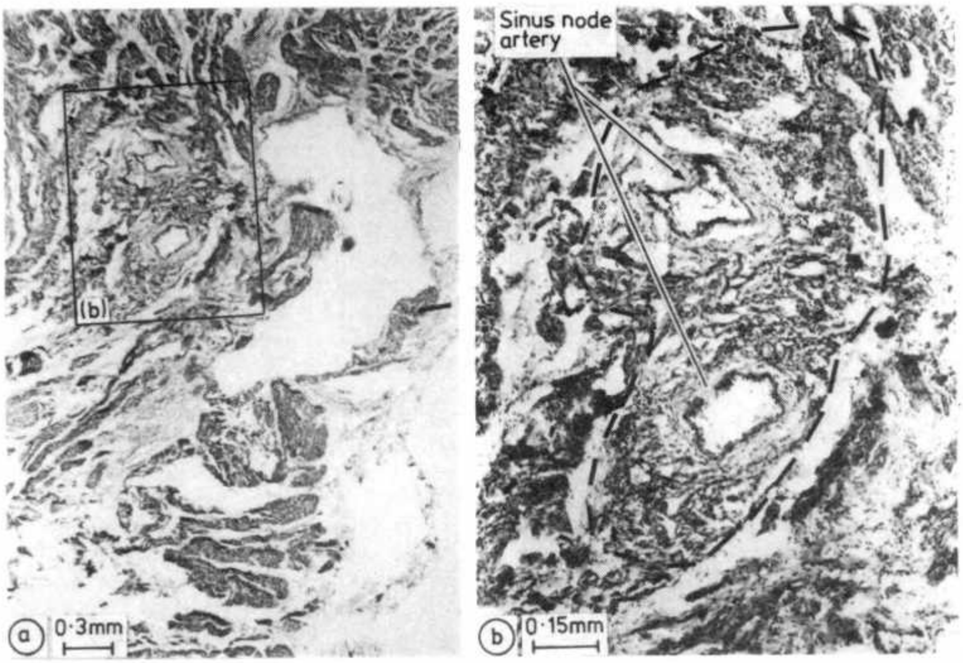

Fig. 1 *Histological appearance of hypoplastic sinus node (case 1) (a) and magnified in (b) to show the few nodal cells surrounding the nodal artery. The extent of the node is marked by broken lines in (b).*

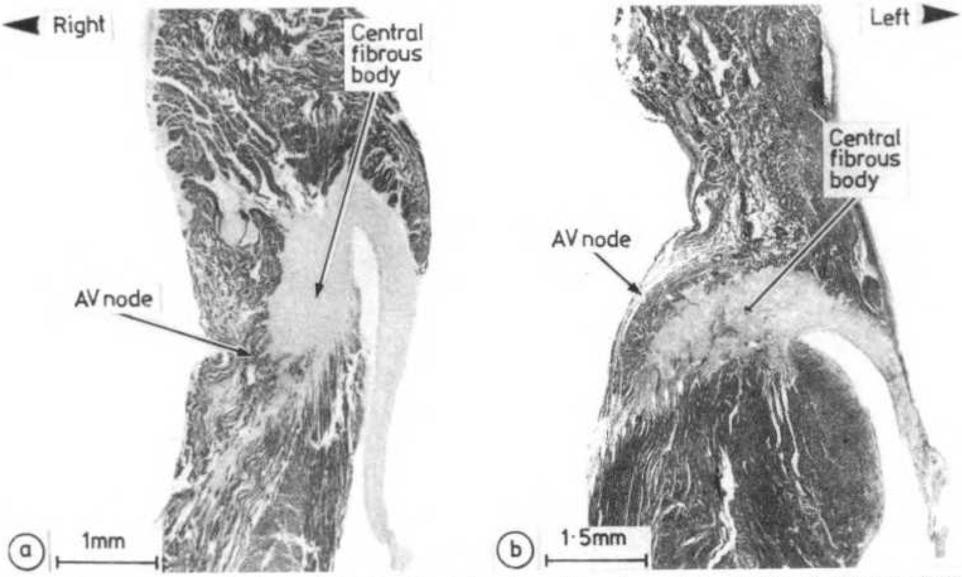

Fig. 2 *Histological appearance of atrioventricular junction in the plane of the atrioventricular (AV) node. The hypoplastic node from the patient in case 1 (a) is compared with that from the normal heart (b) of a 2 day old infant.*

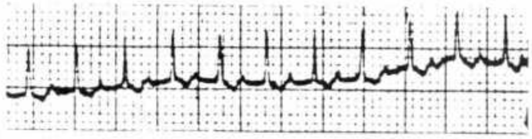

Fig. 3 *Lead II trace of electrocardiogram from the patient in case 2 showing supraventricular tachycardia.*

not respond to the digoxin and verapamil given to the mother. While under observation at 32 weeks' gestation the fetus died in utero. Labour was induced and a hydropic male fetus was delivered by the vertex. On gross examination the heart and great vessels were anatomically normal. The foramen ovale and duct were patent. Histological examination showed a small sinus node located lateral to the superior cavoatrial junction. It was very poorly formed and consisted of only a few nodal cells around a nodal artery (Fig. 1). Its maximum dimensions were 1·1 mm wide and 2 mm long. The atrioventricular node was grossly underdeveloped, although there was a well formed bundle and bundle branches (Fig. 2). Only a few nodal and transitional cells marked the site of the node. The remaining atrioventricular junction was normal.

Case 2

The mother was induced at 34 weeks' gestation for fetal ascites and supraventricular tachycardia. The infant, a boy, developed heart failure with continuing severe ascites and tachycardia (Fig. 3). Cardiac catheterisation showed poor right ventricular function. He responded temporarily to treatment but rapidly succumbed to progressive intractable cardiac failure and died at the age of 3 days.

Postmortem examination of the heart showed no abnormality except the presence of a prominent posteustachian sinus at the inferior cavoatrial junction. The foramen ovale was probe patent, and the ductal wall was thick. The sinus node was situated laterally in the cavoatrial junction and supplied by an anterior artery. The body of the node was small and measured 1·5 mm long and 1 mm wide. There were few nodal cells (Fig. 4). A thin tail of the node could be traced intramyocardially. The atrioventricular node was located in its expected position. There were multiple extensions of conduction tissue into the central fibrous body. The penetrating bundle, branching bundle, and bundle branches were normally situated, but the entire system was smaller than usual. The right bundle branch was tiny. No accessory connexions were seen.

Case 3

A baby was born at term after a normal pregnancy. He gasped initially but did not develop adequate respirations. His electrocardiogram showed a very

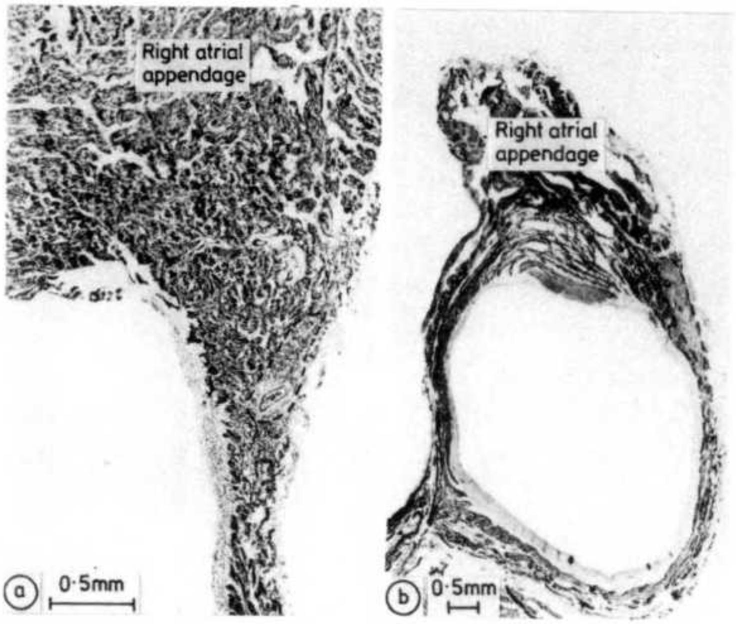

Fig. 4 *Histological appearance of the sinus node (case 2) composed of a small area around the nodal artery (a) compared with a normal node from a newborn infant sectioned in the same plane but shown at a lower magnification (b). The broken lines mark the extent of the nodes.*

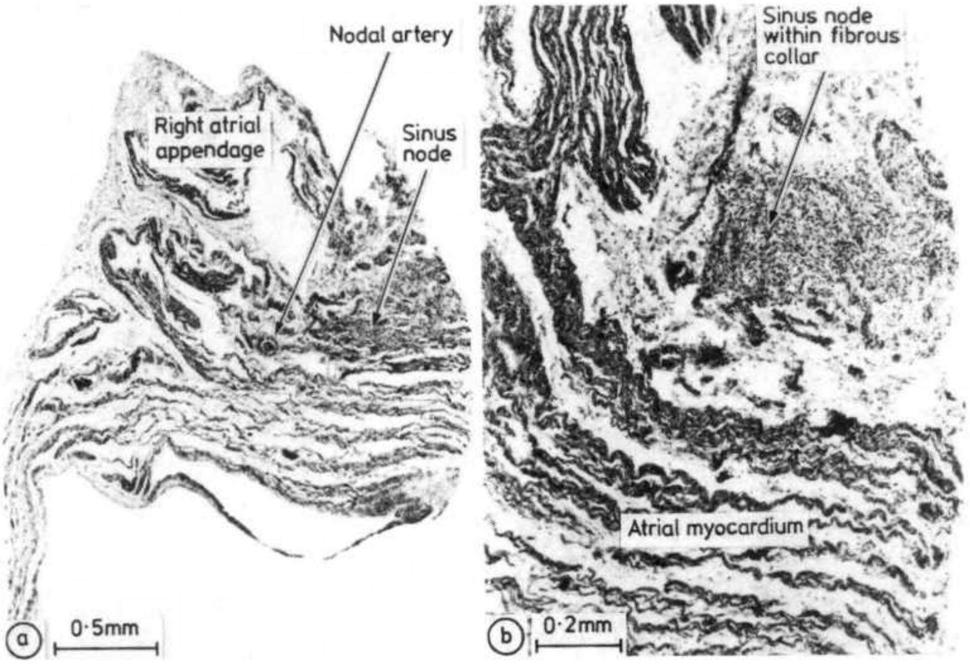

Fig. 5 *Histological appearance of the right cavoatrial junction (case 3) (a) showing the nodal artery which courses within the transitional cells of the node. Another section, inferior to (a), at higher magnification shows the fibrous tissue around the node (b).*

variable rhythm consisting of episodes of supraventricular extrasystoles with intervening periods of bradycardia. Congental heart disease was suspected. The baby died aged 1½ hours despite continuous and appropriate resuscitative measures.

No anatomical abnormalities were noted in the heart, great arteries, or veins at necropsy. The foramen ovale and duct were patent. Histological examination showed a grossly abnormal cardiac conduction system. The sinus node was tiny and located just to the right of the crest of the right atrial appendage. The body of the node measured no more than 0·6 mm long and 0·2 mm wide. It had no direct arterial supply and was insulated in most parts by fibrous tissue from the rest of the atrial myocardium. The sinus node artery skimmed the superior region of transitional cells (Fig. 5). The atrioventricular system was normally distributed proximally but was much smaller than expected. The origins of the bundle branches were tenuous. Anteriorly, a tiny accessory bundle, 12 μm thick and comprising of a few myocardial cells, connected the branching bundle to the left bundle branch (Fig. 6). Examination of the parietal atrioventricular junctional area did not show any further accessory connexions.

Discussion

Arrhythmias in childhood are usually too benign to cause symptoms or too transient to be identified. There is, however, a very small group of children in whom these disturbances in rhythm are persistent and can and do prove fatal. We have recently made a histological examination of the conduction system in three patients in whom the arrhythmias were observed immediately before death. In all three cases there were no gross anatomical abnormalities of the heart which might have potentiated malformations of the conduction system. This absence of anatomical malformation was particularly surprising in the neonate in case 3, in whom the clinical signs suggested "congenital heart disease."

The normal sinus node, unlike that seen in older individuals,[3 4] does not have a strong collagen network. It has been suggested that the collagen framework that separates the nodal cells into small clusters has a part in stabilising the electrical activity of the sinus node.[5] In infants, electrical instability may be partly due to poor formation of the nodal collagen.[6] In our three hearts there was a paucity of fibrous tissue within the sinus node, and the nodal

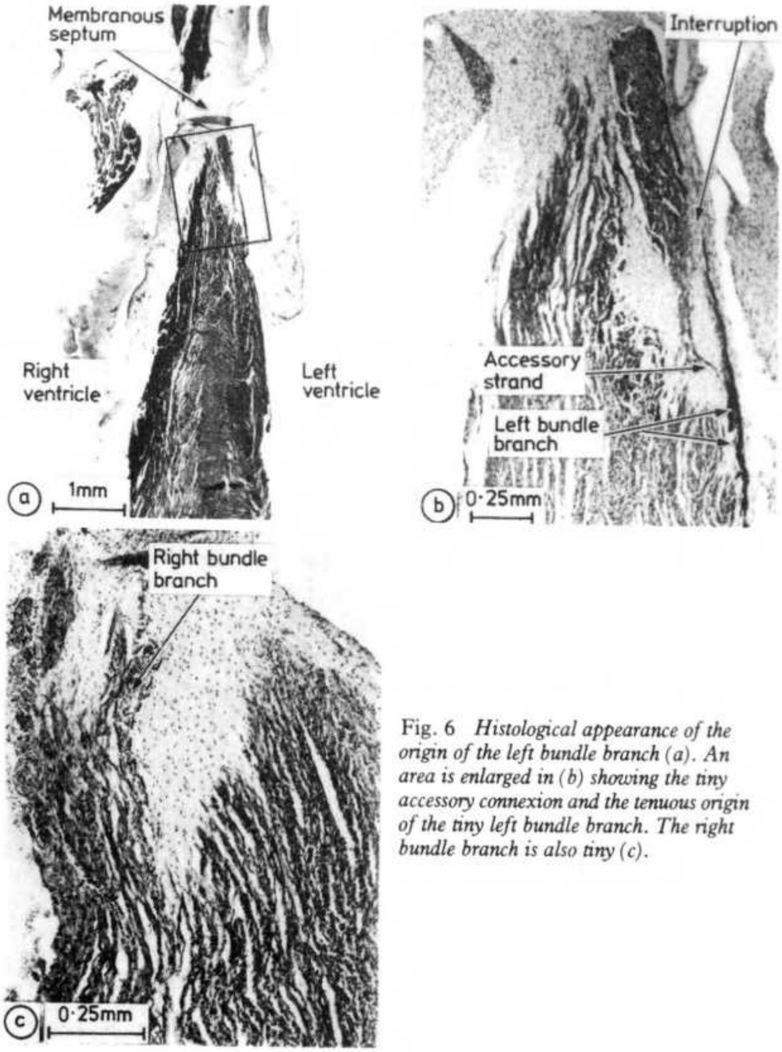

Fig. 6 *Histological appearance of the origin of the left bundle branch (a). An area is enlarged in (b) showing the tiny accessory connexion and the tenuous origin of the tiny left bundle branch. The right bundle branch is also tiny (c).*

cells were not well segregated into groups. More significantly, the sinus nodes in all our cases were notably hypoplastic and lacking in bulk. The dimensions were less than half the normal range for neonates[7] and smaller than for fetuses.[8]

Atrial arrhythmias have been associated with a loss in nodal fibres not accompanied by an increase in connective tissue.[9] The loss in nodal fibres in patients in this study, who ranged from a 2 year old to a patient in his ninth decade, was thought to be due to a degenerative process. In contrast, all our patients were in the perinatal age range. We therefore feel that the hypoplasia of the sinus node in our cases was due to an arrest or a defect in development rather than an active degenerative process.

It seems probable that the sinus node defect could, in itself, have an effect on the heart rhythm. Nevertheless, on its own, this is unlikely to account for the fatal outcome. All our cases had additional poor formation of the atrioventricular conduction axis. In the two cases in which supraventricular tachycardia was noted the atrioventricular node was either hypoplastic or smaller than expected. In the other case, in which the rhythm was variable, the atrioventricular conduction system was also small. A tiny accessory connexion was found between the branching bundle and the left bundle branch. The "arrhythmogenic" potential of this type of bypass tract has previously been suggested.[10] The accessory pathway is exceedingly small, and pathways of this size could possibly have been missed in other cases. Another unusual finding (case 3) was the presence of a fibrous collar around the sinus node (although there was minimal fibrous tissue within the node). The collar permitted only minimal contact of the node with the rest of the atrial myocardium.

In all these cases of arrhythmia we were able to find abnormalities in the conduction system. Nevertheless, at this stage it is not possible to conclude that the arrhythmias were due to the specific defects of the conduction system. There is a clear anatomical correlation with the electrocardiographic findings in ventricular pre-excitation.[11 12] Anatomical correlations with other forms of arrhythmia are exceedingly difficult, although the possibilities are considerable.[13] There is much that needs to be investigated further. For instance, to what extent does hypoplasia of the atrioventricular node influence the heart rate? Is underdevelopment of the cardiac conduction system a major cause of fatal perinatal (particularly supraventricular) tachycardia? We hope that this study will generate more interest and prompt a detailed examination of the cardiac conduction system in all patients with confirmed electrographic changes who subsequently come to necropsy. Only in this way, and by preparing suitable controls, will we be able to evaluate precisely the clinical significance of changes seen under the microscope which otherwise must comprise, at best, circumstantial evidence.

We thank our clinical colleagues for permission to report details of their patients.

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Successful treatment of atrial tachycardias with flecainide acetate

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SUMMARY Intravenous flecainide successfully terminated atrial tachycardia in three patients. Maintenance treatment with oral flecainide prevented the recurrence of tachycardia for up to three years. These results suggest an additional use for flecainide which should be further explored.

Flecainide acetate is a new synthetic antiarrhythmic drug which is classified as a Vaughan Williams class IC agent.[1 2] It has been shown to be effective in the treatment of junctional arrhythmias[3] and in certain ventricular arrhythmias,[4–6] but there are few published data on its use in atrial arrhythmias. It seems effective in the conversion of atrial fibrillation to sinus rhythm, but is much less effective for terminating atrial flutter.[7] We report three patients with atrial tachycardias who were successfully treated by intravenous flecainide and in whom sinus rhythm was maintained with the oral preparation.

Patients and methods

CASE 1

A 23 year old man with the Wolff-Parkinson-White syndrome (type A) underwent successful cryoablation of a left lateral accessory pathway and incidental closure of a persistent foramen ovale. Nine days postoperatively he developed frequent atrial extrasystoles and episodes of atrial tachycardia and fibrillation, with intermittent left bundle branch block. There was no evidence of pre-excitation, and intracardiac electrophysiological studies confirmed the atrial origin of the arrhythmia. Tachycardia became incessant and was not terminated by disopyramide 150 mg given intravenously. Verapamil 5 mg intravenously produced only temporary suppression. On the twelfth postoperative day flecainide 75 mg was given intravenously and completely suppressed tachycardia and the associated atrial ectopic activity. With maintenance treatment with oral flecainide 150 mg twice daily he has remained asymptomatic for three months and his electrocardiogram shows uninterrupted sinus rhythm.

CASE 2

A 57 year old man with an eight year history of recurrent attacks of palpitation and syncope was diagnosed by electrophysiological study as having chaotic atrial tachycardia. Thyroid function tests were normal. Treatment, over a five year period, with digoxin, verapamil, metoprolol, disopyramide, atenolol, sotalol, and propranolol, alone and in combinations of two drugs, proved ineffective at suppressing the attacks. He was readmitted with an episode of tachycardia which had started four days previously. On admission his heart rate was approximately 200 beats/min and blood pressure 95/70 mm Hg. Flecainide, 90 mg intravenously, terminated the tachycardia, but it recurred 30 minutes later at the slower atrial rate of 150 beats/min. A further 75 mg of flecainide was given, which gradually slowed the tachycardia until sinus rhythm emerged. He remained free of symptoms and was in sinus rhythm six months later, taking oral flecainide 150 mg twice daily.

CASE 3

A 33 year old man was admitted with a two year history of palpitation, which lasted from one hour to several days and was occasionally associated with syncope. The attacks had increased in frequency, occurring on alternate days. Prophylaxis with propranolol and disopyramide, either alone or in combination, was ineffective. Resting electrocardiograms showed a narrow QRS complex tachycardia at a rate of 160–170 beats/min and left ventricular hypertrophy on voltage criteria. Thyroid function tests were normal. A first pass nuclear angiogram showed globally impaired left ventricular function, and at cardiac

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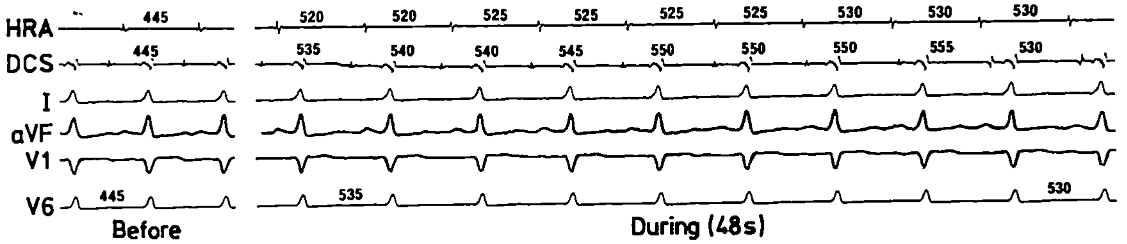

Figure *Electrocardiograms and electrograms showing the effect of intravenous flecainide on automatic left atrial tachycardia (case 3). Before flecainide administration the left atrial focus has a discharge frequency of 135 beats/min (445 ms). During infusion there is gradual slowing of the tachycardia rate with the emergence of sinus rhythm at a rate of 113 beats/min (530 ms) after 48 s. Note the change in atrial activation sequence from earliest activity in the distal coronary sinus electrogram (DCS) before flecainide administration to earliest activity in the high right atrium (HRA) during flecainide infusion.*

catheterisation left ventriculography showed a large cavity with general hypokinesis and ejection fraction reduced at 25%. Intracardiac pressures were normal, as was coronary arteriography.

Electrophysiological study showed an automatic left atrial tachycardia. Intravenous flecainide 120 mg slowed the tachycardia from 135 beats/min, and sinus rhythm resulted after 48 s at a rate of 113 beats/min (Figure).

With maintenance treatment with flecainide 100 mg three times daily he has remained symptom free for three years. Excercise electrocardiograms and 24 hour Holter monitoring have shown normal sinus rhythm.

Discussion

Initial studies of flecainide showed it to be effective against atrial and ventricular arrhythmias induced in experimental animals by either chemical or ischaemic methods.[8 9]

The electrophysiological effects of flecainide have been studied extensively, and in general its effect on conduction is more profound than on refractoriness. In particular, it causes a consistent increase in the PA interval, a measure of the intra-atrial conduction time, by a mean of 22%.[10] Increases in atrial refractoriness have been shown,[10] but these are usually small and fail to reach statistical significance, although Pop *et al* found a significant increase of 17·5%.[11] In the same report flecainide successfully prevented the induction of atrial tachyarrhythmias by programmed stimulation in nine out of 16 patients studied.

Orning reported a single case of chronic atrial tachycardia where temporary suppression of the arrhythmia was achieved by intravenous flecainide.[12] Somani reported the effective suppression of atrial extrasystoles in two out of three patients given flecainide intravenously but found no effect on chronic atrial fibrillation in another two patients.[13] Nathan *et al* treated 10 patients with paroxysmal atrial fibrillation with intravenous flecainide and produced conversion to sinus rhythm in nine.[7] By contrast, in the same report, termination of paroxysmal atrial flutter by intravenous flecainide was achieved in only two out of a further 10 patients, although the atrial rate slowed in all cases and slowing of the ventricular response occurred in nine.

It is of interest that in two cases in the present report tachycardia reversion occurred by progressive slowing until sinus rhythm emerged and resumed control. This is in contrast to the effect of flecainide on junctional re-entrant tachycardias where termination is sudden and where there is a more pronounced effect on the refractoriness of some of the individual tissue components of the junctional re-entrant circuit.[3 10] In case 1 flecainide successfully abolished the repetitive atrial ectopic activity, which suggests that it may also selectively suppress the enhanced automaticity of ectopic foci.

The efficacy of flecainide against atrial tachycardias shown by these cases suggests a potential additional use for the drug, although comparative studies are required to define its precise role.

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Tetralogy of Fallot with major aortopulmonary collateral arteries

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SUMMARY The clinical features of eight patients with tetralogy of Fallot and major aortopulmonary collateral arteries were determined and found to be usually unhelpful in differentiating such patients from those with pulmonary atresia with ventricular septal defect. The point of connection between the pulmonary and collateral arteries could usually be demonstrated at cineangiography by observing washin and washout between the two systems. The central pulmonary arteries connected with the entire pulmonary vascular bed in the five patients in whom the anatomy of the pulmonary circulation was clearly demonstrated and were thought to do so in the remaining three patients also. In six out of eight patients only one collateral artery connected with each hilar pulmonary artery.

These findings suggest that the anatomy of the pulmonary circulation in patients with tetralogy of Fallot and major aortopulmonary collateral arteries is usually less complex than in pulmonary atresia with ventricular septal defect, making the outlook for complete repair more hopeful. The major determinant of successful complete repair appears to be pulmonary arterial size. Early palliative surgery to increase pulmonary blood flow is recommended to encourage normal growth of the central and intrapulmonary arteries.

Unlike in patients with pulmonary atresia and ventricular septal defect the association of tetralogy of Fallot with major aortopulmonary collateral arteries is rare. In pulmonary atresia with major aortopulmonary collateral arteries a successful intracardiac repair depends on the size of the central and intrapulmonary arteries, the absence of stenoses, and the number of lobar and segmental pulmonary arteries connected to the central pulmonary arteries. The anatomy of the pulmonary arterial circulation in patients with tetralogy of Fallot and major aortopulmonary collateral arteries has not been well documented. We therefore describe the clinical and angiographic features in eight such patients.

Patients and methods

Eight patients from this hospital and Killingbeck Hospital, Leeds, had cineangiographic demonstration of tetralogy of Fallot with a patent right ventricular outflow tract and major aortopulmonary collateral arteries. Patients with an acquired collateral circulation were excluded from the study. The earliest date of cardiac catheterisation was 1972. Four patients came from each hospital; five were girls and three were boys.

Details of the clinical presentation, physical signs, cardiac catheterisation and angiographic studies, surgical treatment, and outcome were taken from the hospital records. The cineangiograms were carefully studied in order to delineate the blood supply of each bronchopulmonary segment of lung. The presence of washin and washout was specifically sought to help decide whether a segment of lung had a dual pulmonary blood supply.[1] Several patients were studied at a time when selective injections into the major aortopulmonary collateral arteries consisted of a single large film exposure of a hand injection of contrast medium into the collateral artery. This made it difficult to determine segmental pulmonary arterial blood supply in some patients with absolute confidence.

The central pulmonary arteries and their branches and the collateral arteries and their branches were mapped out on a diagram of the bronchial branching pattern.[2] The size of the pulmonary trunk and central

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and intrapulmonary arteries was assessed. The side of the aortic arch and other intracardiac and extracardiac abnormalities were recorded.

CLINICAL PRESENTATION

The patients presented at between 1 day and 3 years of age. None required urgent treatment, and there was no history of hypoxic spells either at presentation or later during follow up. Mild cyanosis and a murmur were noted in six babies during the first week of life. In one patient mild cyanosis, sweating, and tachypnoea on feeding were noted at 6 weeks. The remaining patient, the oldest in the series, born in 1942, did not present until 3 years of age when she was noted to be mildly cyanosed and short of breath.

Six patients had a prominent continuous murmur, of whom two also had a soft systolic murmur at the left sternal border. One patient had a loud systolic murmur with a thrill at the left sternal border and one only a soft systolic murmur. All had a single second heart sound. An ejection click was heard in three patients. The chest radiograph showed a right aortic arch in six patients. Pulmonary vascular markings were decreased in three, normal in three, and increased in the remaining two patients. In all cases, the electrocardiogram showed right axis deviation and signs of right ventricular hypertrophy. Cross sectional echocardiography was available for only the last two patients and appeared to show pulmonary atresia with ventricular septal defect.

The clinical diagnosis was pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries in six patients. The remaining two patients were thought to have tetralogy of Fallot, one with acquired collateral circulation.

CINEANGIOGRAPHY

Four patients had selective cineangiograms into the major aortopulmonary collateral arteries. All these collaterals arose from the descending thoracic aorta. Table 1 shows their number and distribution. An injection into the right ventricular outflow tract was performed in three patients and an injection into the left pulmonary artery in one (Fig. 1). Injection at these sites combined with selective injections into the major aortopulmonary collateral arteries gave the best definition of the segmental pulmonary arterial blood supply. In those patients with selective cineangiograms it was relatively easy to decide whether or not the major aortopulmonary collateral arteries were in communication with the pulmonary arteries by looking for washin and washout (Fig. 2). This was more difficult in the remaining patients, but if the aortograms were studied carefully washout could sometimes be demonstrated. In five patients the major aortopulmonary collateral arteries were seen connecting with the hilar pulmonary arteries. In those cases the central pulmonary arteries appeared to supply 100% of the bronchopulmonary segments. One patient had an absent left central pulmonary artery, but the right pulmonary artery connected with all the segmental arteries of the right lung and was also perfused by one major aortopulmonary collateral artery which joined the right pulmonary artery at the hilium. In the other two patients it was not possible to be certain of the segmental pulmonary arterial blood supply, but there was a considerable amount of washout at the hilum of both lungs, suggesting that the central pulmonary arteries connected with all the bronchopulmonary segments in each lung.

The central pulmonary arteries were hypoplastic in six patients, and normal in the other two. The intrapulmonary arteries were also small in the six patients with hypoplastic central vessels. In one of the two patients with normal sized central pulmonary arteries, the intrapulmonary arteries of the left lung were smaller than normal (Fig. 1). The presence of a right aortic arch was confirmed in six of the eight patients.

SURGICAL OPERATIONS AND OUTCOME

Five patients (cases 1, 4, 5, 6, and 7) had an aor-

Table 1 *Details of major aortopulmonary collateral arteries*

Case No	*Selective cineangiograms**	*No and site of collaterals*	*Segments supplied by CPA*	*Size of CPA*	*Intrapulmonary arteries*
1	Yes	2: 1 left, 1 right	100%	LPA 5–8 mm	RUL 2–4 mm
2	No	2: 1 left, 1 right	Probably 100%	Normal	Normal
3	Yes	3: 2 left, 1 right	100%	5–8 mm	2–4 mm
4	No	1 right	Right lung 100%, CLPA absent	RPA 5–8 mm	HLPA fills late from bronchial collaterals
5	Yes	2: 1 left, 1 right	100%	5–8 mm	Not well defined but 5–8 mm
6	No	4 or 5: 2 left, 2 or 3 right	Probably 100%	5–8 mm	Not well defined but 5–8 mm
7	Yes	2: 1 left, 1 right	100%	5–8 mm	Not well defined but 5–8 mm
8	No	4: 3 left, 1 right	100%	Normal	5–8 mm on left, normal on right

CPA, central pulmonary artery; CLPA, central left pulmonary artery; LPA, left pulmonary artery; RPA, right pulmonary artery; RUL, right upper lobe; HLPA, hilar left pulmonary artery.
*Of major aortopulmonary collateral arteries.

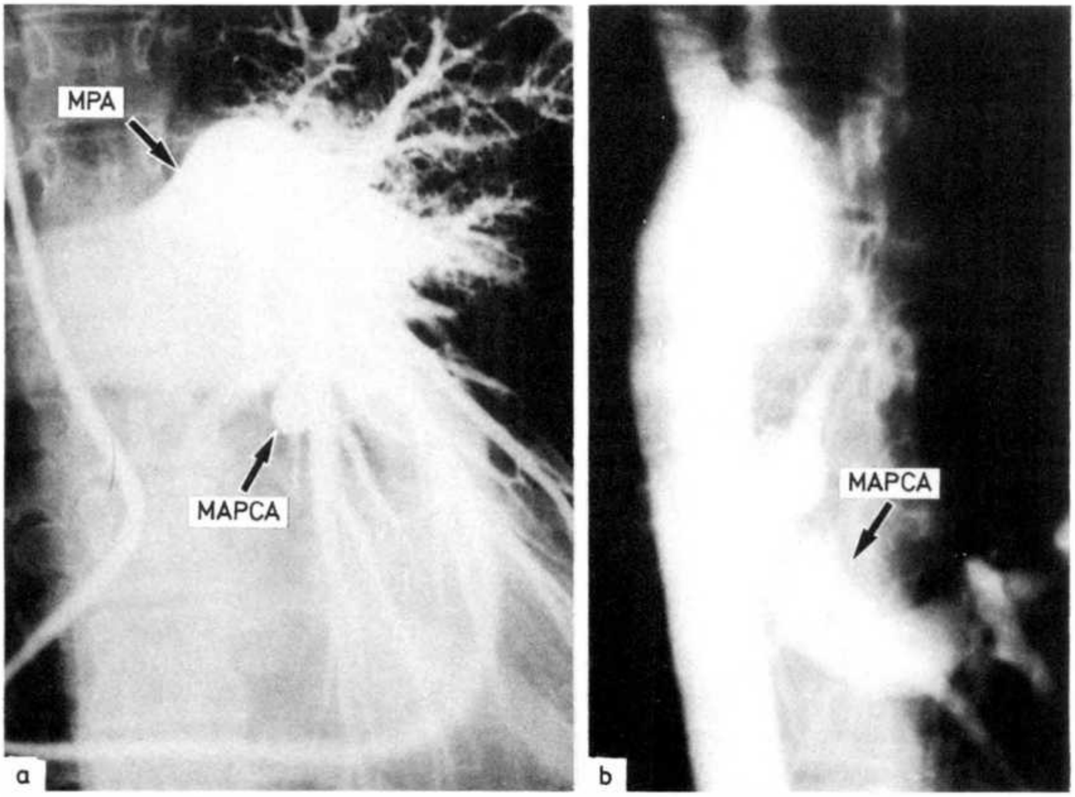

Fig. 1 *Case 8: (a) Cineangiogram of the left pulmonary artery showing a good sized main pulmonary artery (MPA) and right pulmonary artery, but the left intrapulmonary arteries are smaller than normal. A major aortopulmonary collateral artery (MAPCA) can be seen to fill retrogradely. (b) An aortogram showing the major aortopulmonary collateral arteries supplying the left lung.*

ıble 2 *Details of operation and outcome*

se	*First operation*		*Second operation*		*Outcome*
	Age	*Procedure*	*Age*	*Procedure*	
	7½ yrs	Right BT shunt and ligation of collaterals	2 d after first operation	Left modified BT shunt	Awaiting repair
	13 yrs	Ligation of collaterals, left thoracotomy followed by complete repair			Well; residual pulmonary incompetence, no postoperative cardiac catheterisation
	3 yrs	Open infundibulectomy, pericardial patch, no VSD closure	5 yrs	Closure of MAPCA using balloon transaortically during cardiac catheter	Follow up in USA since 1978
	11 mnths	Left BT shunt			Awaiting repair
	2 yrs	Right BT shunt, collateral vessels ligated	3½ yrs	Two collaterals tied via left thoracotomy, then complete repair	Died 14 hours postoperatively, low output
	18 mnths	MAPCA ligated, left BT shunt, thrombosed—reoperation 2 days later	6 yrs	Complete repair (3 hrs to dissect Blalock)	Died 12 hours postoperatively, low output
	3 yrs	Left BT shunt, ligation of collaterals	8 yrs	Revision of left BT shunt	Awaiting repair
	30 yrs	Left collaterals ligated	31 yrs	Complete repair, infundibular resection, no pulmonary valvotomy	Postoperative catheterisation, pulmonary artery pressure 42/6 mm Hg, right ventricular pressure 68/9 mm Hg, residual right MAPCA

, Blalock-Taussig; MAPCA, major aortopulmonary collateral arteries; VSD, ventricular septal defect.

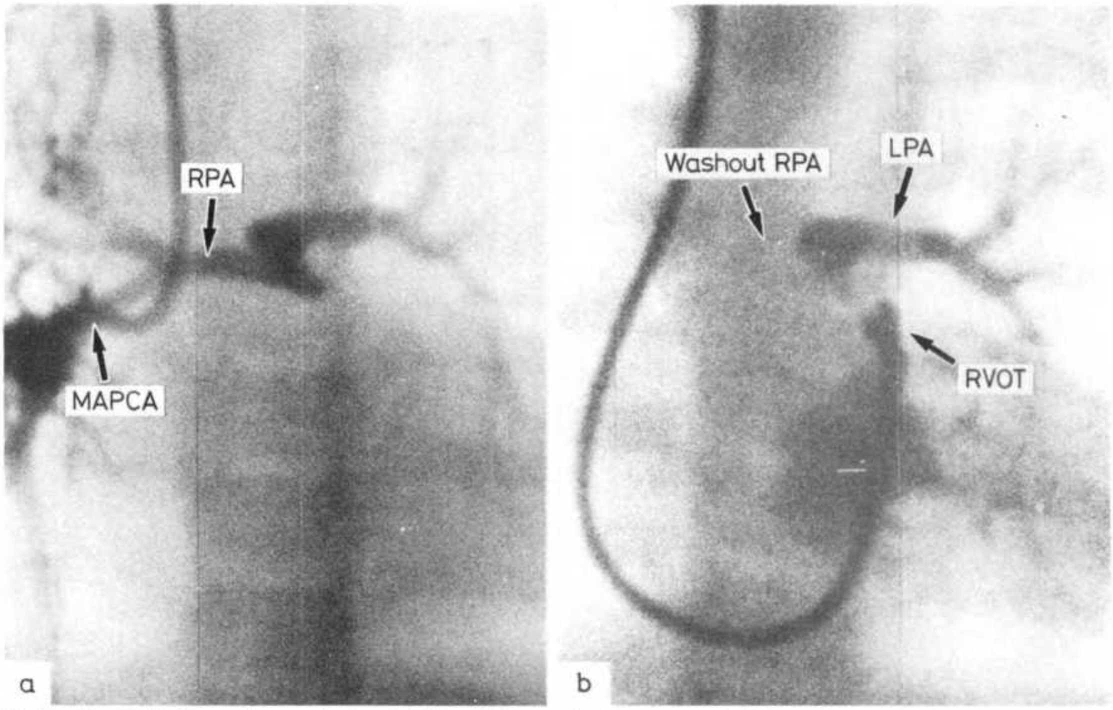

Fig. 2 *Case 5: (a) Cineangiogram showing the filling of the central pulmonary arteries from a selective injection into a major aortopulmonary collateral artery (MAPCA) and (b) washout of the right pulmonary artery (RPA) due to major aortopulmonary collateral artery flow after an injection into the right ventricular outflow tract (RVOT). LPA, left pulmonary artery.*

topulmonary shunt performed (Table 2). None showed appreciable clinical improvement, and in three patients (cases 5, 6, and 7) subsequent cardiac catheterisation did not demonstrate a significant increase in the size of the pulmonary arteries. Collateral arteries were ligated in six patients, at the time of a shunt operation in four. There was no evidence of pulmonary infarction after ligation of a collateral artery in any patient. To date only two patients (cases 2 and 8) have survived a complete repair at the age of 13 and 30 years. These were the only patients with good sized pulmonary arteries. In both these patients the major aortopulmonary collateral arteries were tied, in one some months before the repair and in the other at the time of the repair. Two other patients (cases 5 and 6) died immediately after a complete repair. At necropsy the central pulmonary arteries were small. Both of these patients had previously had a Blalock-Taussig shunt. Three patients had palliative aortopulmonary shunts performed because their pulmonary arteries were small (they will be reinvestigated before an intracardiac repair is considered). The remaining patient (case 3) had an open infundibulectomy with pericardial patch insertion into the right ventricular outflow tract but without closure of the ventricular septal defect. This patient also had balloon occlusion of major aortopulmonary collateral arteries at a subsequent cardiac catheterisation in another institution.[3]

Discussion

This is the first report of a group of patients with tetralogy of Fallot and major aortopulmonary collateral arteries. There have previously been two single case reports describing the association with limited clinical detail and no follow up.[3 4]

The findings in the present study suggest that in contrast to what is seen in most patients with pulmonary atresia and ventricular septal defect, in patients with tetralogy of Fallot all the bronchopulmonary segments are connected to the central pulmonary arteries. Furthermore, the number of collateral arteries arising from the descending thoracic aorta was generally smaller in patients with tetralogy of Fallot than in most patients with pulmonary atresia with ventricular septal defect. In six out of eight cases of tetralogy of Fallot usually only one collateral artery connected with each hilar pulmonary artery. Lastly, since major aortopulmonary collateral arteries are commonly associated with pulmonary atresia with ventricular septal defect, the presence of these collaterals might have been expected to occur only in cases with severe tetralogy of Fallot. In the present study, however, two patients had a relatively mild form of tetralogy of Fallot.

When the patients presented, a significant systolic murmur was often not heard despite the presence of an open right ventricular outflow tract, suggesting a low blood flow across the pulmonary valve. In patients thought to have pulmonary atresia with ventricular septal defect, therefore, it is important to determine whether or not the valve is in fact atretic by selective injection of contrast medium into the right ventricular outflow tract. Non-invasive investigations are not yet helpful in this respect, since it is difficult to distinguish an imperforate pulmonary valve from one that is barely patent by cross sectional echocardiography, at least in our experience. Nevertheless, the introduction of Doppler echocardiography with duplex scanning may make it possible to detect the presence of forward flow across the pulmonary valve. Improvement of near field resolution on cross sectional echocardiography should also help clarify the anatomy of the right ventricular outflow tract. Cineangiography will still be required, however, for demonstrating the pulmonary arterial anatomy and blood supply.

As in pulmonary atresia with ventricular septal defect selective injection into each major aortopulmonary collateral artery is mandatory to determine the source of blood supply. The size of the central and intrapulmonary arteries may be better demonstrated by right ventricular outflow tract or pulmonary arterial injection. In the present series each lung studied appeared to be entirely connected to the central pulmonary artery, but this is a small series. Investigation of these patients with tetralogy of Fallot should therefore aim to exclude the presence of collateral arteries connecting end to end with lobar or segmental pulmonary arteries that do not have an alternative source of blood supply. The investigations should also exclude the presence of a dual blood supply to a part of the lung by two or more collaterals, in addition to the supply from the right ventricular outflow tract.

As is the case in pulmonary atresia with ventricular septal defect, when all or most bronchopulmonary segmental arteries connect to the central pulmonary arteries, a successful intracardiac repair depends on the size of the central and intrapulmonary arteries. The only two patients in the present series to have had a successful repair were those with normal sized pulmonary arteries. Palliative surgery should aim at encouraging normal growth of the pulmonary arteries. The choice is between an aortopulmonary shunt and reconstruction of the right ventricular outflow tract. There is some uncertainty about which procedure is the more effective, particularly as it is not known whether the results in patients with pulmonary atresia can be extrapolated to those with a patent right ventricular outflow tract. The timing is, however, probably at least as important as the type of palliative surgery. Early palliative surgery is recommended since it is more likely to achieve growth rather than mere distension of the central and intrapulmonary arteries. Recent studies have shown that not only small but large central pulmonary arteries can be associated with hypoplastic intrapulmonary arteries in patients with tetralogy of Fallot without collaterals and with either pulmonary atresia or tetralogy of Fallot and major aortopulmonary collateral arteries.[5 6]

In the future the management of patients with tetralogy of Fallot and major aortopulmonary collateral arteries may be modified by using transcatheter embolisation of the collateral arteries when the flow through the pulmonary valve is satisfactory, for example with detachable balloons.[3] In this way, a lateral thoracotomy might be avoided in patients destined for a complete repair. In patients who require palliative surgery the major aortopulmonary collateral arteries could be embolised at cardiac catheterisation after the surgical procedure if the central pulmonary artery supplied most or all of each lung and pulmonary blood flow was adequate. This approach has the advantage that a preliminary trial occlusion of the collateral artery is possible,[7] while monitoring systemic arterial saturation and watching for any other possible complications of collateral occlusion.

In conclusion, patients with tetralogy of Fallot and major aortopulmonary collateral arteries require a precise cineangiographic diagnosis and demonstration of the anatomy of the pulmonary circulation in order to plan the surgical management. Surgical treatment will have to be individualised, as in patients with pulmonary atresia and ventricular septal defect. Nevertheless, since the anatomy of the pulmonary circulation appears to be less complex in patients with tetralogy of Fallot than in those with pulmonary atresia and ventricular septal defect, management will usually consist of encouraging normal growth of the central and intrapulmonary arteries by increasing the pulmonary blood flow as a prelude to complete repair. The outlook may be more optimistic in patients with tetralogy of Fallot since they have an open right ventricular outflow tract and all or most bronchopulmonary segments appear to be connected to the central pulmonary arteries.

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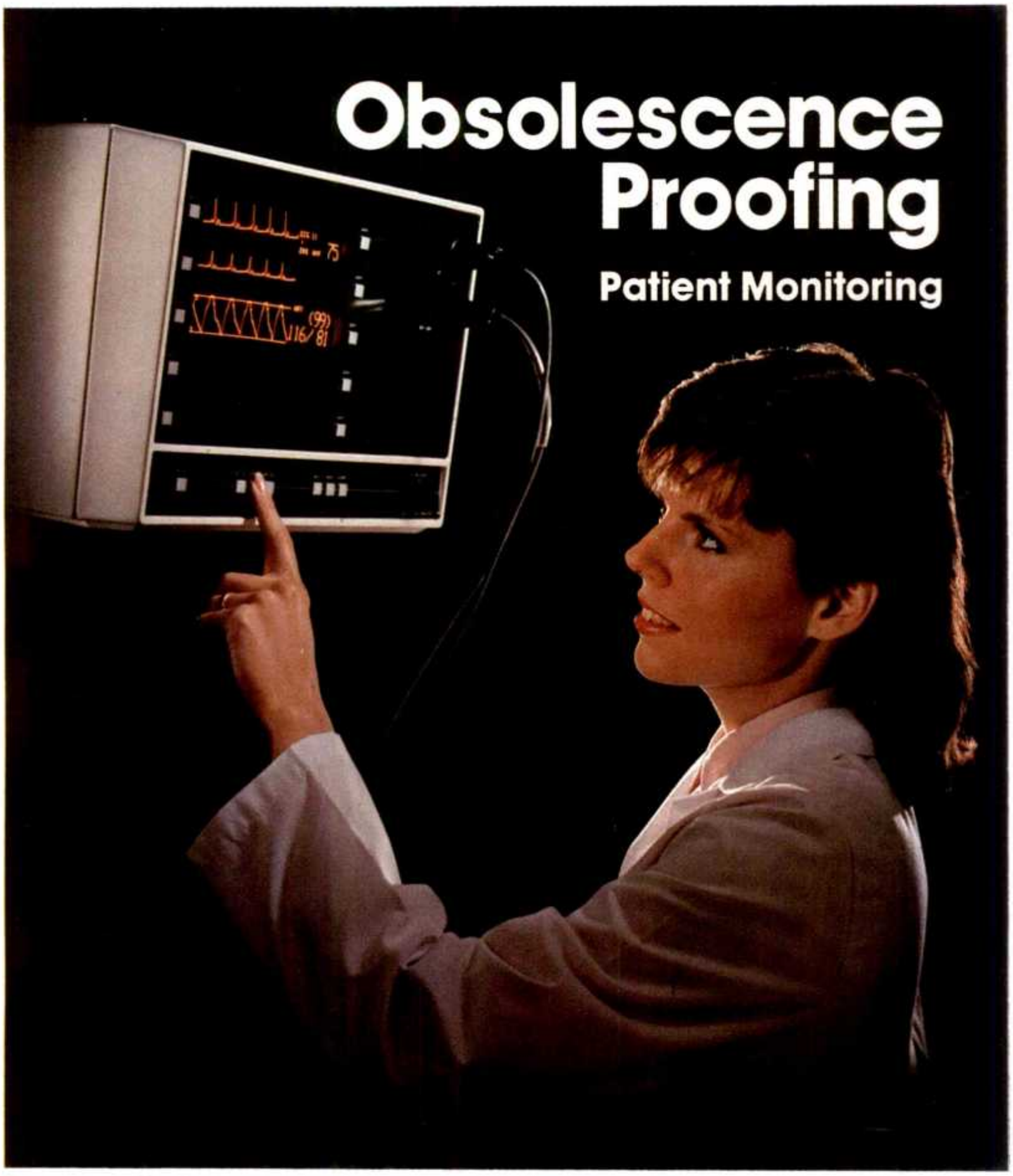

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Prostacyclin infusion in patients with acute myocardial infarction

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SUMMARY To investigate whether prostacyclin protects ischaemic myocardium in humans the effect of prostacyclin or placebo was studied in two groups of patients with acute myocardial infarction who presented within six and 16 hours of the onset of symptoms. Intravenous infusion of prostacyclin or placebo was started immediately after admission at a rate corresponding to 4–5 ng/kg/minute. The infusion was maintained for 72 hours. Clinical status, electrocardiograms, plasma enzyme activity, infarct extension during the infusion, and reinfarction after the infusion were studied. Prostacyclin was well tolerated by most patients: neither systemic blood pressure nor heart rate differed between the two groups. In the 11 patients who received treatment within six hours of the onset of symptoms prostacyclin significantly lowered the maximum plasma activities of creatine kinase MB and lactate dehydrogenase. In the 19 patients who received treatment 6–16 hours after the onset of symptoms prostacyclin had no such effect. None of the patients receiving prostacyclin had an extension of the infarction during the infusion, whereas four patients receiving placebo did; this difference was significant.

These data are the first to provide evidence that prostacyclin might limit myocardial injury in patients with acute myocardial infarction.

Prostacyclin is a metabolite of arachidonic acid that is formed in vascular endothelium throughout the body.[1-3] Prostacyclin has vasodilative and platelet antiaggregatory properties, and in view of these actions the compound may prevent platelet aggregation and thrombosis in healthy vessels. Vascular formation of prostacyclin is reduced in atherosclerosis,[4-6] and this has been proposed as a factor responsible for the increased incidence of thrombosis in this state.

The actions mentioned above have also prompted the proposal of prostacyclin as a suitable agent for the treatment of acute myocardial infarction. The findings concerning endothelial production of prostacyclin in healthy and atherosclerotic vessels suggested that such treatment might restore lost prostacyclin activity in the cardiovascular system, especially in the coronary circulation. In fact, prostacyclin reduces the size of experimental infarction in various animal models.[7-10] On the other hand, the administration of prostacyclin to humans with various signs of ischaemic heart disease has yielded inconclusive results.[11-13]

To evaluate the effect of prostacyclin in patients with acute myocardial infarction, we performed a double blind investigation in 30 patients.

Patients and methods

The study was performed during 1983-84 at this hospital. Patients admitted to the hospital coronary care unit and meeting the selection criteria of the study were invited to participate. Informed consent was obtained from all patients. The study protocol was approved by the local human investigations committee.

SELECTION OF PATIENTS

Patients admitted with chest pain typical of acute infarction (>30 min duration) and with confirmative electrocardiogram or plasma enzyme activity or both were included provided that treatment could be

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started within 16 hours of the onset of symptoms. The age limits were 18–75 years; female patients were included only if postmenopausal. Either (*a*) new or presumably new Q waves of at least 0·04 s duration and amplitude amounting to >25% of the following R wave in either (i) leads II, III, and aVF, (ii) leads I and aVL, or (iii) two or more precordial leads, or (*b*) ST segment elevation of >2 mV in two leads were the confirmative electrocardiographic criteria used. A rise in plasma activity to at least twice the upper normal limit of the hospital laboratory's reference value for two of the enzymes—creatine kinase, aspartate aminotransferase, and lactate dehydrogenase—or appreciably increased myocardial specific creatine kinase MB activity was accepted as evidence of acute myocardial infarction.

Patients with an earlier acute myocardial infarction within the past two months, as well as those with psychiatric, endocrinological or infectious or malignant diseases, were excluded.

RANDOMISATION AND STRATIFICATION

A randomisation protocol was prepared before the study and was kept by the pharmacist delivering the drug to the coronary care unit during the entire investigation. The randomisation protocol was adapted to yield 15 patients in each of the prostacyclin and placebo groups. The investigation protocol also prescribed a separate study to compare the results of patients receiving prostacyclin with those receiving placebo within six hours of the onset of symptoms. These patients were, however, not randomised separately.

ADMINISTRATION OF PROSTACYCLIN OR PLACEBO

Prostacyclin (synthetised by the Upjohn Company and formulated by the Wellcome Foundation), stored as a freeze-dried powder, was dissolved in glycine buffer pH 10·5 immediately before infusion. A fresh solution was prepared every 12 hours during the infusion period. Glycine buffer at pH 10·5 was infused as the placebo. The infusion was given into a peripheral arm vein using a volume controlled pump (IMED 922) at a rate corresponding to 1 ng/kg/min and increased stepwise over one hour to a maximum of 5 ng/kg/min. If systolic blood pressure fell or heart rate increased by >10% before the maximum infusion rate had been reached the infusion was maintained at the current rate. The overall infusion time was 72 hours. During the last four hours the infusion rate was gradually tapered off in order to avoid rebound phenomena. In addition to the infusion of prostacyclin, the patients received routine clinical and pharmacological treatment for acute myocardial infarction and were managed by the ordinary staff of the coronary care unit. The investigators did not influence the routine care.

EVALUATION OF CLINICAL STATUS AND LABORATORY FINDINGS

All patients underwent a baseline clinical and laboratory evaluation before infusion of the drug was started comprising a physical examination, a standard 12 lead electrocardiogram, chest *x* ray examination, routine chemical blood examination, and measurement of plasma activity of creatine kinase MB, creatine kinase, aspartate aminotransferase, and lactate dehydrogenase. During the infusion of prostacyclin a 12 lead electrocardiogram was recorded daily. Plasma creatine kinase MB activity was measured in samples taken 8, 16, and 24 hours after the start of the infusion. Plasma creatine kinase, aspartate aminotransferase, and lactate dehydrogenase activities were measured daily until discharge. At the end of the study (30 days after admission) a physical examination, including evaluation of the patient's functional status, and an electrocardiogram were performed. The 12 lead electrocardiograms were analysed using a QRS scoring system[14] in which each recording was scored from 0 to 29, with a value >2 strongly suggesting myocardial infarction. QRS scoring was performed on electrocardiograms recorded on days 3, 7, and 30 after the start of the infusion. ST segment elevation was measured as the sum of the vertical distances between the isoelectric line and the midpoint of the ST segment in the two leads showing the most prominent elevations on day 1. ST elevation was assessed on days 1, 2, and 3 after the start of the infusion. All electrocardiographic evaluations were performed by a trained interpreter who was not a member of the investigating team and was unaware of the type of treatment the patients had received.

Results

COMPARABILITY OF THE GROUPS

Table 1 shows the result of the randomisation procedure. The number of patients, their sex distribution and age, as well as the time from the onset of symptoms to the start of infusion did not differ between the prostacyclin and placebo groups. The number of patients receiving infusion within six hours of the onset of symptoms was slightly greater in the prostacyclin group. Some patient characteristics related to an increased incidence of ischaemic heart disease were over-represented in the prostacyclin group, but the difference is not significant. Table 2 shows the number of patients receiving beta blocking drugs before or during the infusion of prostacyclin or placebo. The proportion of patients given beta blocking drugs did not differ between the two groups. The

Table 1 *Group characteristics in patients with acute myocardial infarction randomised to receive prostacyclin or placebo and the occurrence of factors related to increased incidence of myocardial infarction in the two groups. Figures are numbers of patients*

	Prostacyclin	*Placebo*
Group characteristics		
No of patients	15	15
Sex distribution (M/F)	10/5	12/3
Age (yr)		
Mean (SEM)	62 (6)	60 (3)
Range	53 (71)	40 (73)
Mean (SEM) time from onset of pain to start of infusion (h)	8·1 (1·2)	9·6 (1·3)
Infarct localisation (anterior/posterior)	8/7	8/7
No of patients receiving infusion within six hours of onset of symptoms	7	4
Infarct localisation (anterior/posterior)	2/5	3/1
Related factors		
Smoking	12	9
Hypertension	8	6
Hyperlipidaemia	2	3
Earlier angina	6	3
Cardiac failure before infusion	7	3

proportion of patients receiving beta blocking drugs was in fact slightly higher in the placebo group, and this tendency was reinforced during days 2 and 3 of infusion. The difference did not, however, reach statistical significance.

DRUG TOLERANCE

Of the patients in the prostacyclin group, 12 could be given the drug at a rate of 5 ng/kg/minute without exceeding the predetermined systolic blood pressure value or pulse rate. In one patient the infusion rate was never increased above 4 ng/kg/minute because of a tendency to hypotension, and in two other patients the rate had to be reduced to 4 ng/kg/minute for the same reason. Figure 1 shows the values for the systolic and diastolic blood pressure and heart rate. There were no differences in these variables before, during, or after the infusion. Table 3 shows the cardiac stress index (the product of the systolic blood pressure and the heart rate) during the infusion in the two groups. Again there was no difference between the groups.

CLINICAL OBSERVATIONS

Table 4 shows the occurrence of congestive heart failure before and after the study. Two patients were receiving treatment for heart failure when they entered the study; both were in the prostacyclin group. Another five patients in this group had clinical or radiographic findings or both indicating heart failure on entering the study. The number of patients in the prostacyclin group requiring treatment for heart failure did not increase during the course of the infusion. In the placebo group three patients had clinical or radiographic evidence of heart failure on entering the study. During the course of the infusion, this number increased to eight (Table 4).

Table 2 *Administration of beta blocking drugs in the groups receiving prostacyclin or placebo. Figures are numbers of patients (mean 24 hour dosages in mg given in parentheses)*

Drug	*Time (h)**	*Preinfarction*	*Day 1*	*Day 2*	*Day 3*
Prostacyclin group					
Metoprolol	0–16	1 (200)	1 (200)	4 (125)	4 (125)
	0–6	1 (200)	1 (200)	2 (175)	2 (175)
Pindolol	0–16	1 (10)	1 (10)	1 (10)	1 (10)
	0–6	0	0	0	0
Atenolol	0–16	1 (100)	1 (100)	1 (10)	1 (10)
	0–6	0	0	0	0
None	0–16	12	12	9	9
	0–6	6	6	5	5
Placebo group					
Metoprolol	0–16	1 (100)	2 (125)	7 (107)	7 (121)
	0–6	0	0	4 (75)	3 (83)
Alprenolol	0–16	2 (400)	2 (400)	2 (400)	2 (400)
	0–6	0	0	0	0
Timolol	0–16	0	0	0	1 (20)
	0–6	0	0	0	0
Practolol†	0–16	0	0	0	0
	0–6	0	1 (15)	0	0
None	0–16	12	10	5	4
	0–6	4	3	0	1

*From onset of chest pain to start of infusion.
†Given intravenously.

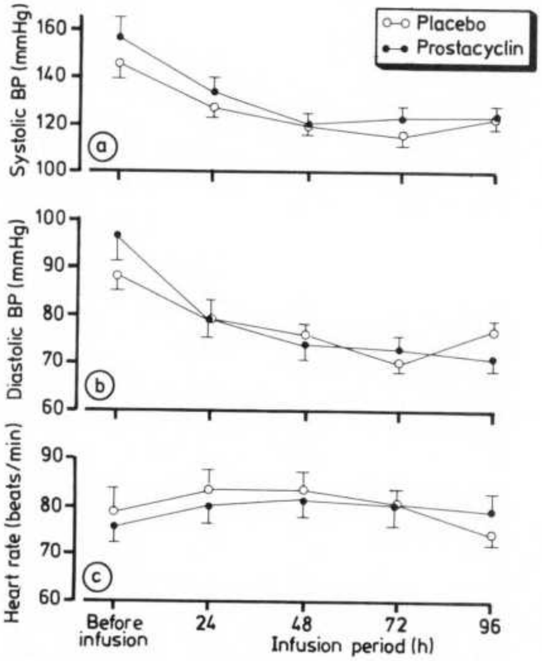

Fig. 1 *(a) Systolic and (b) diastolic blood pressure (BP) and (c) heart rate from 0–96 hours after the onset of intravenous infusion of prostacyclin (4–5 ng/kg/min) or placebo during 72 hours in patients with acute myocardial infarction.*

Table 3 *Cardiac stress index (expressed as the product of systolic blood pressure (mm Hg) and heart rate (beats/min)) before (day 0), during (day 1–3), and after (day 4) infusion of prostacyclin (4–5 ng/kg/min) or placebo in patients with acute myocardial infarction. Values are mean (SEM)*

	Prostacyclin	*Placebo*
Day 0	11677 (1248)	11756 (1268)
Day 1	10313 (896)	11647 (928)
Day 2	10572 (770)	10437 (787)
Day 3	9857 (519)	9172 (711)
Day 4	9307 (420)	9828 (585)

Table 4 *Occurrence of congestive heart failure (CHF) among patients treated for acute myocardial infarction with prostacyclin or placebo. Figures are numbers of patients*

	Prostacyclin	*Placebo*
Treatment of CHF:		
Before study	2	0
After infusion	6	8
Signs of CHF:		
Before study	7	3
After infusion*	2	5

*Additional patients.

Table 5 *Occurrence of infarct extension, reinfarction, and deaths in patients with acute myocardial infarction treated with prostacyclin or placebo. Figures are numbers of patients*

	Prostacyclin	*Placebo*
Extension of infarction (during the infusion)	0*	4
Reinfarction (after the infusion)	2	0
Deaths	0	1

*Significant difference from the placebo group: ($p<0.05$) (Fisher's exact test, one tailed).

EXTENSION OF INFARCTION AND REINFARCTION

Extension of the acute myocardial infarction, as evidenced by a new episode of typical chest pain in conjunction with a new rise in plasma creatine kinase MB or creatine kinase activity, occurred during the infusion in three patients receiving placebo. In addition, another patient receiving placebo, having improved clinically during the initial 24 hours of infusion, developed persistent pain for more than 12 hours and a fatal ventricular rupture on day 2; this case was also regarded as an extension of the infarct. None of the patients receiving prostacyclin developed similar signs of infarct extension during the infusion (Table 5). This difference in infarct extension (4 *vs* 0) is significant ($p<0.05$, Fisher's exact test, one tailed). From the end of the infusion until day 30, none of the

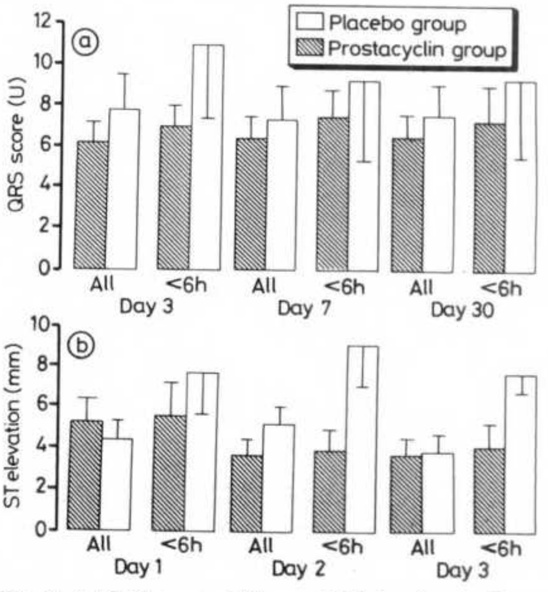

Fig. 2 *(a) QRS score and (b) sum of ST elevations in all patients with acute myocardial infarction infused with prostacyclin (4–5 ng/kg/min) or placebo during 72 hours and in patients receiving infusion within six hours (<6 h) after the onset of symptoms. Values are mean (SEM).*

patients in the placebo group developed reinfarction. In the prostacyclin group, two patients developed a reinfarction in the same area as that injured initially (on day 6 and 21).

LABORATORY FINDINGS

Figure 2 shows the QRS score and sum of ST elevations in the two groups. The QRS score was slightly but not significantly lower on all occasions in the patients receiving prostacyclin, both in the groups as a whole and in those receiving an infusion within six hours of the onset of symptoms. The sum of ST elevations did not show any uniform pattern in the group as a whole but tended to be lower in the prostacyclin group in patients receiving an infusion within six hours of onset of symptoms.

The maximum plasma activity of creatine kinase MB, creatine kinase, aspartate aminotransferase, and lactate dehydrogenase did not differ between the groups as a whole (Fig. 3). Nevertheless, in the patients who received an infusion within six hours of the onset of pain both plasma creatine kinase MB and lactate dehydrogenase activity was significantly ($p<0.05$ and 0·05 respectively) lower (Fig. 3).

The time course of the release of enzymes in the patients receiving an infusion within six hours of the onset of pain was also determined (Fig. 4). During the first 24 hours of infusion the increase in creatine kinase MB activity was smaller in the prostacyclin group than in the placebo group, as was the increase in plasma lactate dehydrogenase activity (Fig. 4). The initial mean value did not differ between the groups, but the peak value was lower in the prostacyclin group. Interestingly, after the end of the infusion lactate dehydrogenase activity reached almost identical values in the prostacyclin and the placebo groups.

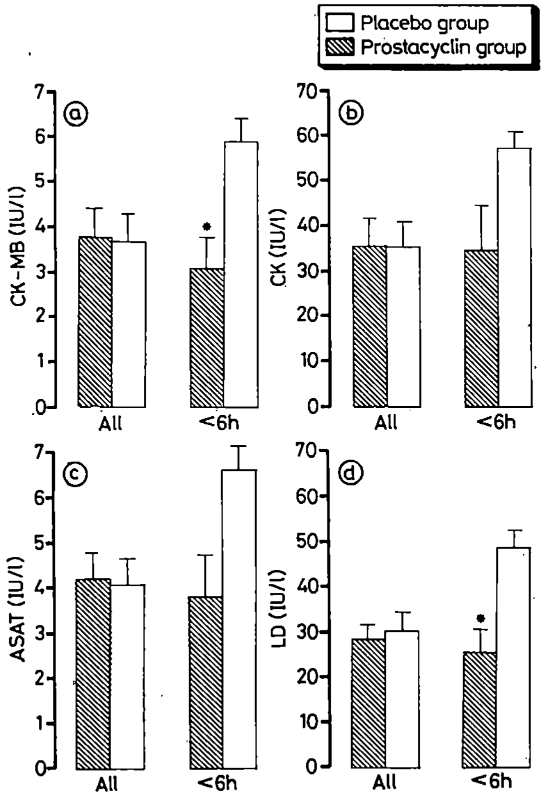

Fig. 3 *Peak plasma activities of (a) myocardial specific creatine kinase (CK-MB), (b) total creatine kinase (CK), (c) aspartate aminotransferase (ASAT), and (d) lactate dehydrogenase (LD) in all patients with acute myocardial infarction treated with prostacyclin or placebo and in patients receiving infusion within six hours (<6 h) after the onset of symptoms.* p<0·05, significant difference from placebo group.*

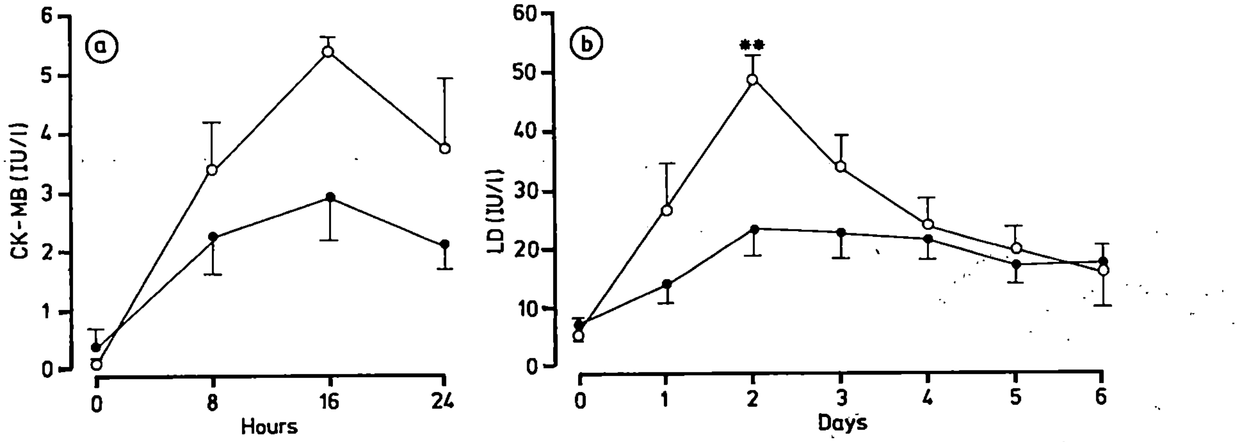

Fig. 4 *Plasma enzyme activity in relation to time in patients with acute myocardial infarction given prostacyclin (●) or placebo (○) within six hours after the onset of symptoms: (a) plasma activity of myocardial specific creatine kinase (CK-MB) immediately before (0 hours) and during the first 24 hours of infusion of prostacyclin or placebo and (b) plasma activity of lactate dehydrogenase (LD) in the same patients in the basal state (day 0) and during the first six days after the onset of symptoms.** p<0·01, significant difference from prostacyclin group.*

Discussion

Patients receiving prostacyclin within six hours of the onset of symptoms had significantly lower maximum plasma activity of creatine kinase MB and lactate dehydrogenase than the placebo group. We regard these lower values for plasma creatine kinase MB and lactate dehydrogenase activity in the prostacyclin group as indicating smaller infarcts among these patients compared with the placebo group. As evident from Fig. 3 the patients receiving early placebo infusion had higher maximum plasma creatine kinase MB, creatine kinase, aspartate aminotransferase, and lactate dehydrogenase activities than the group as a whole. This is probably because patients with larger infarctions—and hence higher maximum plasma enzyme values—experience more pronounced symptoms and therefore present earlier. The proportion of patients with anterior wall infarctions was greater in the placebo group; whether or not this may have influenced the data cannot be judged at present. The proportion of patients taking beta blocking drugs was not higher in the prostacyclin group. Thus the observed difference in plasma enzyme activity between the groups can hardly be explained by a more active beta blocking regimen in the prostacyclin group. A direct cardioprotective action of prostacyclin in acute myocardial infarction therefore seems possible.

In addition to the differences in maximum plasma creatine kinase MB and lactate dehydrogenase activities, the time courses of the plasma activity of these enzymes are notable. Thus the curve for creatine kinase MB activity in the prostacyclin group was flatter than in the placebo group. In addition, the peak of the plasma lactate dehydrogenase curve in patients infused with prostacyclin within six hours was lower than in those given placebo. Interestingly, the plasma lactate dehydrogenase values in the prostacyclin group were numerically lower during the entire infusion, approaching those in the placebo group after the infusion.

Another important finding was that patients receiving prostacyclin appeared to be protected against infarct extension during the infusion. This was evidenced by a significantly lower incidence of infarct extension in patients receiving prostacyclin than in those receiving placebo. The lower incidence of infarct extension seems to accord well with the observed lower maximum plasma creatine kinase MB and lactate dehydrogenase activities discussed above, in as much as they indicate that myocardium at risk at the onset of the infusion is protected by the active drug and, consequently, that enzyme release and a possible tendency to infarct extension are depressed. If this hypothesis is correct patients receiving prostacyclin should run an increased risk of reinfarction after the infusion. The incidence of reinfarction tended to increase in the present group of patients receiving prostacyclin; two developed reinfarction after the infusion compared with none of the patients who had received placebo; the difference was, however, not significant.

A drug with vasodilative activity, like prostacyclin, can be expected to induce a decrease in peripheral vascular resistance and a reflex increase in cardiac output. The latter is certainly not desirable in acute myocardial infarction since the increase in cardiac output may require more dynamic work by the heart. In the present study prostacyclin did not affect blood pressure and heart rate more than placebo—that is, with the infusion rate limits applied in the present study the drug probably does not interfere appreciably with the central haemodynamics. Bradycardia was not a general finding in the placebo group, probably because the patients were not routinely given beta blocking drugs during the acute phase. Furthermore, prostacyclin did not induce cardiac failure or even aggravate signs of failure. In fact all patients in the placebo group with signs of cardiac failure before infusion also required treatment for this afterwards; in addition, five more patients in this group developed evidence of cardiac failure during the infusion. In contrast, of the seven patients in the prostacyclin group who had signs of cardiac failure before the infusion, three did not require treatment afterwards.

Although the present study points to a beneficial effect of prostacyclin in patients with acute myocardial infarction, the possible underlying mechanism is unknown. Since a myocardial saving effect of prostacyclin is indicated in patients receiving treatment within six hours of the onset of symptoms some conceptually related postinfusion treatment (that is, treatment aimed to counteract platelet aggregation and formation of thromboxane A2) should be given that can keep salvaged myocardium in a metabolic condition that allows contractile work to be maintained. In men with unstable angina aspirin has been shown to protect against acute myocardial infarction and death[15]; this drug should be effective also in the present situation, in which myocardium at risk may persist after the infusion of prostacyclin.

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Submaximal exercise testing early after myocardial infarction

Difficulty of predicting coronary anatomy and left ventricular performance

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SUMMARY Impaired left ventricular function and extensive coronary artery disease are important determinants of prognosis after acute myocardial infarction. The ability of clinical and predischarge submaximal exercise test variables to predict multivessel coronary artery disease and impaired left ventricular function was assessed in 62 survivors of acute myocardial infarction. Abnormal exercise blood pressure response and short exercise performance were predictors of multivessel disease, but exercise induced ST segment changes and clinical variables were not. Q wave infarction, high grade Killip classification, and exercise induced ST segment elevation predicted statistically significant impairment of resting left ventricular function, whereas other clinical and exercise test variables did not.

Exercise induced ST segment changes were therefore of little value in detecting extensive coronary disease, although exercise induced ST elevation was an indicator of poor resting left ventricular function. Although abnormal exercise haemodynamics may detect extensive coronary artery disease, other physiological markers of reversible myocardial ischaemia are probably necessary to plan optimal management in these patients.

The single most important predictor of adverse prognosis after myocardial infarction is a reduced left ventricular ejection fraction.[1-3] The presence of extensive coronary artery disease may be an important independent predictor of cardiac complications in those patients with moderate rather than severe impairment of left ventricular performance.[2-4]

We therefore analysed the ability of exercise testing early after infarction, together with simple clinical factors of known adverse prognostic significance, to predict left ventricular performance and coronary anatomy. The exercise test variables studied were those previously reported to define groups of patients at risk of subsequent complications: exercise induced ST depression,[5-7] inability to complete a submaximal exercise protocol,[8] an abnormal blood pressure response to submaximal exercise,[9] and exercise induced ST elevation.[10 11]

Patients and methods

STUDY GROUP

The study group consisted of 62 patients (58 men, four women; age range 29–64 (mean 53·8) years) who had performed submaximal exercise tests between 7 and 23 (mean 10·8) days after acute myocardial infarction and in whom coronary anatomy was known. In 60 patients coronary anatomy had been established by coronary arteriography and in two at necropsy. The study group was derived from a total of 131 patients aged ≤65 years admitted to hospital between May 1981 and August 1982 who fulfilled at least two of the following criteria: (*a*) typical chest pain lasting longer than 30 minutes; (*b*) increase in serum creatinine kinase and lactate dehydrogenase activity to more than twice the upper limit of the hospital normal ranges, with a typical evolutionary pattern on serial estima-

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tions; and (*c*) evolutionary electrocardiographic changes. Q wave infarction occurred if the electrocardiographic changes included the development of new Q waves of at least 0·04 s duration and >25% of the amplitude of the subsequent R wave and was classified as anterior if new Q waves occurred in any of leads I, aVL, V1 to V6 or as inferior if new Q waves occurred in at least two of leads II, III, or aVF.

During the time this investigation was in progress 43 patients with acute infarction did not undergo early exercise testing because of death in hospital (16), persistent heart failure (3), previous coronary artery bypass surgery (5), intractable angina requiring early surgery (2), various non-cardiac diseases (9), or patient inability or physician refusal to undertake exercise testing at this time (8). A further 26 patients with infarction performed the early exercise test but were not studied by cardiac catheterisation because they did not fulfil any of the indications for this procedure—namely: exercise induced ST depression, angina during follow up, or young age in asymptomatic patients.

All the patients with exercise induced ST depression underwent left ventricular angiography and coronary arteriography six weeks after infarction except for two who died before their planned readmissions. One of these, who had sustained inferior myocardial infarction, had severe widespread disease in all the major coronary arteries at postmortem examination and was included in the data analysis. In the other, who had both ST depression and elevation induced by submaximal exercise after anterior infarction, necropsy was not performed. Twenty seven patients without exercse induced ST depression underwent left ventricular angiography and coronary arteriography (median time 6 (range 3–56) weeks) after acute myocardial infarction. Fourteen were investigated because of symptoms, and 13 asymptomatic patients (mean age 45·6 years) were investigated to aid prognostic assessment. A man who died suddenly six months after inferior infarction had severe multivessel coronary disease at necropsy and was included in the data analysis. No patient had recurrent myocardial infarction before angiography.

EXERCISE TESTING

Exercise testing was performed according to a modified Naughton protocol[12] using a constant treadmill speed of 2 mph, with the initial treadmill grade of zero increasing by 3·5% at the end of each two minute stage. This protocol is designed so that the oxygen consumption required increases by approximately one metabolic equivalent (about 3·5 ml/kg/min) with each two minute stage, starting with a workload of two metabolic equivalents. Twelve lead electrocardiograms were recorded at rest, at the end of each two minute stage, immediately after exercise, and at one minute intervals thereafter for a minimum period of five minutes or until the resting electrocardiographic pattern had been regained. A three lead rhythm strip was recorded continuously throughout exercise and recovery periods. Cuff blood pressure was recorded at rest, at the end of each two minute stage during exercise, and at one and four minutes after termination of exercise.

ST segment depression or elevation induced by exercise was defined as at least 0·1 mV depression or elevation of the ST segment respectively compared with the resting tracing, measured 0·06 s after the QRS complex in three consecutive complexes with a stable baseline.

End points for the submaximal exercise tests were: eight minutes exercise, the workload of the final two minute stage being five metabolic equivalents; exceeding 70% of the maximum predicted heart rate for age; induction of angina; undue fatigue or dyspnoea; induced ST segment depression of more than 0·5 mV; serious ventricular arrhythmias, or a fall in systolic blood pressure of ≥20 mm Hg from peak values during exercise. An inadequate blood pressure response to exercise was defined as an increase in systolic blood pressure of ≤10 mm Hg during exercise, with peak systolic blood pressure being <140 mm Hg, or a decrease in systolic blood pressure of ≥20 mm Hg during exercise.[9]

At the time of exercise testing all the patients were ambulant without chest pain and free of clinical and radiological signs of heart failure. Heart failure during the acute infarction period that had subsequently resolved was not a contraindication to exercise testing.

Normal drug treatment was continued on the day of the submaximal exercise tests. Ten of the 62 patients were receiving beta blocking agents: three were taking antihypertensive drugs before hospital admission and seven had beta blockade instituted in the periinfarction period. An attempt was made to minimise any effect of this by performing exercise tests as long as possible after the last dose whether the frequency of dosage was once or twice daily. No patient was taking digitalis.

CARDIAC CATHETERISATION

Coronary arteriography and left ventriculography were performed using standard Sones techniques. Multiple coronary angiograms in planes of varying obliquity, including cranial caudal views in both right and left anterior oblique planes, were obtained. Coronary anatomy was assessed by agreement between two observers, at least one of whom did not know the outcome of the preceding exercise test. Stenotic lesions of >70% luminal diameter in one projection, or >50% in two or more projections, were considered significant as these criteria are commonly used to assess the suitability of a vessel for coronary artery bypass grafting.[13] Stenoses in major diagonal or obtuse marginal vessels were considered to constitute left anterior descending or left circumflex coronary artery disease respectively. Patients were classified according to the presence or absence of multivessel coronary disease—that is, significant stenoses in at least two of the three major coronary arteries—thereby avoiding some of the problems of assessing the relative importance of two vessel and three vessel disease in patients with major individual variations in coronary anatomy. Left ventricular angiography was obtained in the 30° right anterior oblique plane and left ventricular ejection fraction determined by the area-length method[14] using a Vanguard XR 80 LV analyser.

DATA ANALYSIS

The relations between the presence of multivessel coronary disease and resting left ventricular ejection fraction and clinical and exercise test variables were determined. The clinical variables assessed were a history of previous myocardial infarction, Killip classification[15] of the index infarction, and cardiomegaly, which required a cardiothoracic ratio of $>50\%$ on the predischarge chest *x* ray film. Differences between the means of independent observations were assessed by Student's *t* test and the differences between proportions by the χ^2 test with Yates's correction.

Table 1 *Clinical and exercise test variables related to the presence or absence of multivessel coronary disease. Figures are numbers of patients (n=62)*

	Present	*Absent*
Site of infarction:		
Anterior	14	6
Inferior	22	7
Non-Q wave	7	6
Previous infarction	8	1
Killip classification		
I or II	37	15
III or IV	6	4
ST depression:		
Total		
Present	25	9
Absent	18	10
After anterior infarction:		
Present	4	2
Absent	10	4
After inferior infarction:		
Present	17	4
Absent	5	3
After non-Q wave infarction:		
Present	4	3
Absent	3	3
ST elevation:		
Present	15	5
Absent	28	14
Inadequate blood pressure response:		
Present	18	1
Absent	25	18**
Inability to complete 5 metabolic equivalents:		
Yes	27	6
No	16	13*

$^{*}p<0{\cdot}05$; $^{**}p<0{\cdot}01$.

Table 2 *Left ventricular ejection fraction (LVEF), according to clinical and exercise test variables. Values are mean (SD) (n=60)*

	LVEF(%)
Site of infarction:	
Anterior (n=20)	47·9 (15·3)
Inferior (n=27)	49·3 (12·0)
Non-Q wave (n=13)	59·5 (10·9)*
Previous infarction:	
Yes (n=8)	53·0 (17·2)
No (n=52)	50·7 (13·1)
Cardiomegaly:	
Present (n=13)	44·7 (15·7)
Absent (n=47)	52·5 (12·8)
Killip classification:	
I or II (n=51)	52·4 (13·4)
III or IV (n=9)	43·8 (11·8)*
Multivessel coronary disease:	
Yes (n=41)	50·5 (14·0)
No (n=19)	52·2 (12·9)
ST depression:	
Present (n=33)	50·8 (14·0)
Absent (n=27)	50·6 (13·1)
ST elevation:	
Present (n=20)	43·2 (13·3)**
Absent (n=40)	54·9 (11·8)
Inadequate blood pressure response:	
Present (n=18)	48·4 (15·5)
Absent (n=42)	52·2 (12·1)
Inability to complete 5 metabolic equivalents:	
Yes (n=31)	48·7 (15·0)
No (n=29)	53·4 (11·2)

$^{*}p<0{\cdot}05$; $^{**}p<0{\cdot}01$.

Results

The only statistically significant predictors of multivessel coronary disease among the clinical and exercise test variables were an abnormal blood pressure response to submaximal exercise or limited effort capacity (Table 1). There was a trend towards multivessel disease in patients with previous myocardial infarction and in those with exercise induced ST depression after inferior myocardial infarction, which did not reach statistical significance. Exercise induced ST depression was a poor predictor of multivessel disease overall, as was exercise induced ST elevation.

Q wave infarction and high grade Killip classification were the clinical variables which were significantly associated with reduced left ventricular ejection fraction (Table 2). Of the exercise test variables, only exercise induced ST elevation predicted poor resting left ventricular function (Table 2). Patients with multivessel coronary disease did not have worse left ventricular function as a group than those who did not.

Twenty nine of the 34 patients who had exercise induced ST depression had this change confined to leads other than those which showed ischaemic changes during the evolution of the acute infarction if transient ST depression in remote leads is considered reciprocal and not primarily ischaemic in origin. Conversely, all 20 patients with exercise induced ST elevation had this change induced in leads with acute infarction changes. Of these 20 patients with exercise induced ST elevation, 16 had anterior and four inferior infarction, and in 18 of the 20 exercise induced ST elevation was confined to leads bearing Q waves.

None of the 10 patients receiving beta blockers had exercise limited by excessive heart rate response. Nevertheless, the proportions of patients who had other exercise test variables were similar to those of patients not receiving beta blockers: limited by angina (10% *vs* 8%) or fatigue (20% *vs* 10%), exercise induced ST depression (40% *vs* 58%) or elevation (20% *vs* 35%), and inadequate blood pressure response (20% *vs* 33%). None of these differences was significant.

Discussion

There is a high prevalence of extensive coronary artery disease in survivors of acute myocardial infarction. We have shown that ST depression induced by a submaximal exercise test before hospital discharge after acute myocardial infarction was a poorer indicator of the presence of multivessel coronary disease than previously reported.[10 16–19] Clinical variables were similarly poor predictors of multivessel coronary disease. An abnormal haemodynamic response to submaximal exercise in the form of limited effort capacity or an abnormal exercise blood pressure response predicted multivessel disease. Importantly, however, the absence of an abnormal haemodynamic exercise response was not a good indicator of the absence of multivessel disease. When resting left ventricular ejection fraction was considered, Q wave infarction and high grade Killip classification were clinical factors which were statistically significant predictors of impaired left ventricular function. A reduced resting left ventricular ejection fraction was also associated with exercise induced ST elevation but not exercise induced ST depression nor other exercise variables.

Patients in this series were consecutive survivors of acute myocardial infarction who had ST depression induced by early submaximal exercise testing or whom were investigated because of symptoms or young age. Ideally, the coronary anatomy would be investigated in every patient who survived myocardial infarction, but this is clearly difficult on many grounds, and studies of the type we report here are confined to selected series.[10 16–19] The prevalence of multivessel disease among our patients was very similar to that in other reported series,[4 20 21] and it is unlikely that differences between our findings and those of other workers can be attributed to different proportions of patients with multivessel disease.

It is also of interest that the incidence of angina, ST depression, fatigue, and abnormal blood pressure changes with exercise was similar in a small group of patients receiving beta blockers and in the remaining patients. We therefore consider it is unlikely that the results can be explained by differences in medication, either within our own series or by comparison with other published results.

CORONARY ANATOMY

Exercise testing early after myocardial infarction has been used to predict the presence of multivessel coronary disease.[10 16–19] Each of these studies has reported results in selected populations: survivors of uncomplicated infarction,[16 17 19] consecutive patients fulfilling specified criteria but an undefined proportion of the total number of patients with acute myocardial infarction,[10] and non-consecutive patients who were investigated by coronary arteriography to assess postinfarction angina or "to assess the extent of coronary disease and left ventricular performance."[18] Criteria for a positive exercise test, and hence a predictor of multivessel disease, have included ST segment depression alone,[19] ST depression or exercise induced angina or both,[10 17 18] or inability to complete a very low workload exercise test protocol because of the occurrence of angina, ST segment changes, or ventricular arrhythmias.[16] In this series, if exercise induced ST depression early after myocardial infarction was considered a positive exercise test result for the detection of multivessel coronary disease predictive values of positive and negative tests were lower than previously reported (Table 3). Several factors might explain this difference. Dillahunt and Miller excluded patients unable to complete their low workload treadmill protocol for "non-cardiac reasons."[16] Survivors of inferior myocardial infarction, the site in which exercise induced ST depression may be most

Table 3 *Comparison of predictive values of positive and negative exercise tests for the prediction of multiple vessel coronary disease*

	No of patients	*Positive* (%)*	*Negative (%)*
Dillahunt and Miller 1979[16]	28	76	73
Schwartz *et al* 1981[10]	48	90	42
Fuller *et al* 1981[17]	40	87	72
Starling *et al* 1981[18]	57	88	69
Akhras *et al* 1982[19]	61	98	88
Present study	62	74	36

*See text for definition.

sensitive for detecting multivessel disease, comprised more than half the total number of patients (21/40) reported by Fuller *et al.*[17] Nearly a third (15/48) of the patients described by Schwartz *et al* had sustained non-Q wave infarction and nearly a quarter (5/21) of their positive exercise tests were so described because of exercise induced angina, without induced ST depression.[10] The importance of exercise induced angina for detecting multivessel coronary disease was stressed by Starling *et al.*[18] Their predictive accuracy for submaximal exercise detection of multivessel disease was 82% if exercise induced ST depression or angina was considered positive but fell to 60% if ST depression alone was analysed. Nevertheless, this difference in the definition of a positive exercise test would not have altered our results because only five of our 62 patients had angina induced by submaximal exercise, all of whom also had exercise induced ST depression. The most impressive correlation between a positive exercise test early after myocardial infarction and multivessel coronary disease has been that of Akhras *et al.*[19] Their young survivors of uncomplicated infarction performed a symptom limited, rather than submaximal, exercise test a mean time of two weeks after the acute infarction. A positive test required exercise induced ST depression of at least 0·15 mV. The use of a symptom limited exercise test protocol may have contributed to the very high accuracy of their exercise tests in predicting multivessel disease, although heart rate limited and symptom limited exercise tests conducted early after acute myocardial infarction have a similar yield of exercise induced ST depression.[22] As these authors themselves point out[19] it may not be appropriate to extrapolate their results to all survivors of acute myocardial infarction.

There are usually major persisting electrocardiographic abnormalities after acute myocardial infarction. In our patients exercise induced ST depression occurred predominantly in leads other than those which showed evolutionary changes of acute myocardial infarction. As the anterior wall of the heart is the area which is best mapped by the standard 12 lead electrocardiogram this may explain why exercise induced ST depression occurred more often after inferior infarction than after anterior infarction.

Advocates of the non-invasive prediction of multivessel coronary disease early after myocardial infarction suggest that this affords a method of selecting patients for early coronary arteriography,[10 17–19] presumably as a prelude to coronary artery bypass surgery in those with suitable anatomy. Akhras *et al* suggest that the same criteria for selecting patients for surgical revascularisation should be used after infarction as in patients with angina,[19] in whom surgery may offer improved prognosis in the presence of three vessel coronary artery disease.[13] Nevertheless, this last multicentre study included patients who were not only symptomatic but had left ventricular ejection fractions >50%, thereby excluding any patient with significant left ventricular damage and many with preceding myocardial infarction. Therefore, the benefits of surgical treatment in survivors of myocardial infarction with multivessel disease who have greater impairment of left ventricular function remain uncertain.[1]

LEFT VENTRICULAR PERFORMANCE

Exercise induced ST elevation was a poor predictor of multivessel coronary disease. Mean resting left ventricular ejection fraction was, however, significantly lower in the group of patients with ST elevation induced by submaximal exercise but not in the group with exercise induced ST depression. Similar results have been reported.[10] Nevertheless, a reduced resting left ventricular ejection fraction has also been found in patients with exercise induced ST depression.[17] The importance of ST elevation induced by exercise after myocardial infarction is controversial,[23 24] but it may be an indicator of an increased probability for future complications.[10 11] The lower left ventricular ejection fractions in our patients with exercise induced ST elevation suggest that this group of patients has more extensive myocardial damage and this may result in a worse prognosis. As left ventricular ejection fraction was similar in each of the two groups who had sustained either anterior or inferior infarction, it seems unlikely that exercise induced ST elevation was merely a marker of anterior infarction, although it occurred predominantly in this group.

An abnormal blood pressure response to submaximal exercise early after myocardial infarction is reported to predict multivessel disease in association with reduced left ventricular ejection fraction.[18] Using the same definition of inadequate blood pressure response to exercise and a similar exercise protocol, we found that this variable predicted multivessel coronary disease but could not confirm a lower resting left ventricular ejection fraction of statistical significance in this group, although there was a trend in this direction. Inability to complete the submaximal exercise protocol predicted multivessel coronary disease in our patients, together with a trend towards greater impairment of resting left ventricular function. We did not measure left ventricular ejection fraction during exercise. This is more likely to correlate with poor exercise performance than variables measured at rest. The association of extensive coronary artery disease with abnormal exercise haemodynamic response is consistent with reports that poor exercise duration and abnormal blood pressure response to exercise early after infarction may be of adverse prognostic significance.[8,25]

CLINICAL IMPLICATIONS

It has been suggested that a suitable screening procedure to select those survivors of acute myocardial infarction who should undergo coronary arteriography might be the performance of an exercise test early after infarction, followed by gated blood pool imaging in those who have ST depression induced by exercise, to exclude those with severe left ventricular damage from invasive investigation.[26] Our data suggest that exercise testing based on ST segment changes is a poor predictor of multivessel coronary disease unless haemodynamic factors are considered. Even then a large proportion of survivors of acute myocardial infarction with multivessel disease will not be detected. It is unlikely, however, that survivors of myocardial infarction with multivessel disease and similar degrees of resting left ventricular functional impairment have a uniform prognosis. It may be more appropriate to use other physiological measurements, such as thallium scintigraphy,[27] which are more specific detectors of reversible regional myocardial ischaemia to determine prognosis and select appropriate surgical or medical management or both.

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Morphology of ambulatory ST segment changes in patients with varying severity of coronary artery disease

Investigation of the frequency of nocturnal ischaemia and coronary spasm

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SUMMARY The frequency and magnitude of objectively determined myocardial ischaemia during normal daily activities of patients with varying severity of coronary artery disease are unknown. Furthermore, the incidence of nocturnal resting myocardial ischaemia and frequency of coronary spasm in patients with normal coronary arteries and chest pain are also not known. One hundred consecutive patients with chest pain referred for coronary angiography were therefore investigated with exercise testing and ambulatory ST segment monitoring. Fifty two of 74 patients with significant coronary artery disease and six of 26 with no significant coronary narrowing had episodes of ST segment change during 48 hours of ambulatory monitoring. Two patients, one with normal coronary arteries and localised spasm and one with three vessel disease, had episodes of ST segment elevation, whereas all other patients had episodes of ST segment depression. The frequency, duration, and magnitude of ST segment changes were greater in patients with more severe types of coronary artery disease. Thus more than six episodes of ST segment change per day occurred in patients with two or three vessel disease or left main stem stenosis and in the only patient with coronary spasm and normal coronary arteries. Nocturnal ischaemia occurred in 15% of patients with coronary artery disease and was almost an invariable indicator of two or three vessel coronary artery disease or left main stem stenosis. Episodes of ST segment change occurred most commonly during the morning hours and least commonly during the night, in parallel with changes in basal hourly heart rates. The heart rate at the onset of ST segment change tended to be lower in patients with coronary artery disease than in those with normal coronary arteries. The duration of exercise to ST segment depression tended to be shorter in patients with more severe disease, but it could not predict patients with nocturnal myocardial ischaemia, left main stem stenosis, or coronary spasm, whereas ambulatory ST segment monitoring was able to identify most of these patients.

Several non-invasive techniques have been used in clinical practice for diagnosing the presence and severity of coronary artery disease.[1 2] A typical history of chest pain and an abnormal resting electrocardiogram are sometimes sufficient to diagnose the presence of coronary artery disease, but its severity cannot be determined by this means. Exercise testing and radioisotope imaging have been used to determine the presence of disease in those patients in whom the history is atypical and the resting electrocardiogram normal.[1–3] Exercise testing also determines the functional consequence of coronary artery disease, and radioisotope scanning provides an index of the size of the ischaemic myocardium, but the severity of underlying coronary artery disease often cannot be determined.[1 4] Ambulatory electrocardiographic ST segment monitoring has been used in several recent studies[5–14] to identify the frequency of myocardial ischaemia in patients with coronary artery disease, but the type and extent of these changes in patients with differing severity of coronary artery disease have not been fully evaluated.

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Improvements in the recording and reproduction of low frequency signals in ambulatory electrocardiographic systems[15] have provided an opportunity to study ST segment changes in different groups in the population. This study was designed to investigate in detail the frequency, duration, magnitude, and morphology of ST segment shifts in consecutive patients undergoing diagnostic coronary arteriography. We determined the frequency of daytime and nocturnal rest angina and of coronary artery spasm in patients with significant coronary artery disease. We also studied the relation between heart rate changes and the onset of ST segment shifts during ambulatory monitoring and compared them with heart rate changes at the development of ST segment depression during conventional exercise testing.

Patients and methods

STUDY POPULATION

We studied 100 (74 men, 26 women; mean (SD) age 53·2 (9) years) consecutive patients with chest pain undergoing diagnostic coronary arteriography who were referred to one consultant cardiologist at this hospital between June 1982 and March 1983. Patients with atrial fibrillation, severe conduction defects on the electrocardiogram, gross left ventricular hypertrophy, those taking digoxin, and those with severe valvar heart disease were excluded. The duration of chest pain was <3 months in seven patients, 2–12 months in 16, and >1 year in 77. Ninety one patients complained of chest pain which was considered typical of angina pectoris and nine had atypical chest pain. A history of previous myocardial infarction with electrocardiographic evidence of Q waves or extensive loss of R wave was present in 27 patients, and a further 21 patients had ST-T wave abnormalities on the resting electrocardiogram. Informed consent was obtained from all patients.

STUDY PROTOCOL

After admission to hospital, all the patients antianginal medications were withdrawn for a period of 48 hours before investigations were started. Glyceryl trinitrate was given for pain. Patients were encouraged to be mobile around and outside the hospital during the period of the study unless they were experiencing frequent chest pains with minimal activity. Forty eight hour ambulatory monitoring and exercise testing were performed, and angina diaries were kept by all patients.

AMBULATORY MONITORING

A two channel recording was obtained using two pairs of bipolar electrodes which were applied precordially. In all patients one channel recorded lead CM5 with the indifferent electrode over the manubrium and the exploring electrode in the precordial 5 position. The other channel recorded inferior changes resembling aVF in 35 patients with the exploring electrode at the xiphisternum and the indifferent electrode at the left sternoclavicular joint; in the other 65 patients the second channel recorded inferior forces by an arrangement in which the indifferent electrode was placed on the right of the manubrium and the exploring electrode over the left iliac fossa: the appearances resemble those seen in lead II. In all patients, a ground electrode was placed over the lower ribs on the right. Electrode jelly and gauze were used initially to abraid the skin until a sufficiently low skin impedance reading was obtained using an Oxford X1–1 electrode impedance tester. Monitor leads were attached to the electrodes (Red Dot 3M) and secured with adhesive tape. A 24 hour, two channel recording was then obtained on magnetic tape using a frequency modulated recorder (Oxford Medilog 2, frequency response 0·05–40 Hz). The tapes were then visually analysed at 60 times normal speed (Oxford Medilog MA20 scanner) and the areas of interest printed out at 25 mm/s.

Significant ST segment depression was defined as planar or downsloping shift of the ST segment of ⩾1 mm in magnitude measured 0·08 s after the J point and persisting for at least 30 s. Significant ST segment elevation was defined as an upward shift of the ST segment of ⩾1 mm in magnitude at the J point compared with the resting recording. At the beginning of each recording in 50 patients, the electrocardiogram was recorded with the patient in various positions, including standing, sitting, lying, supine, and in the left and right lateral positions, and after hyperventilation. None of the patients developed significant ST segment depression with changes of posture, but T wave changes occurred commonly and changes in T wave vector were not regarded as evidence of myocardial ischaemia unless they were also accompanied by significant ST segment shift. The electrocardiogram immediately preceding ST segment change, at the onset of ST segment change, and at the time of chest pain was printed out and heart rate measurements were made.

ANGINA DIARIES

Patients were instructed to keep diaries during the 48 hour monitoring period, during which they noted the time of onset and severity of chest discomfort and the activity at the time of pain. An event button was also pressed at the time of the onset of chest pain, which marked the magnetic tape so that the electrocardiographic playback would automatically display the electrocardiogram at that time.

EXERCISE TESTING

Exercise testing was performed in 99 of the 100 patients on a treadmill according to the modified Bruce protocol. Twelve lead electrocardiograms were recorded before and at the end of every three minutes during the test. More frequent recordings were made if the patient developed chest pain, hypotension, or significant ST segment depression. Blood pressure was measured with a mercury sphygmomanometer. The test was considered positive if there was ST segment depression of ≥1 mm in magnitude which was planar or downsloping and persisted for 0·08 s after the J point. One patient was having frequent pain at rest with ST segment changes and was therefore not exercised. Maximal exercise tests were performed using a treadmill during which exercise was limited by the appearance of chest pain, dyspnoea, fatigue, multiple ventricular extrasystoles, or hypotension.

ANGIOGRAPHY

Contrast left ventriculography and coronary arteriography were performed to obtain five views of the left coronary and at least two views of the right coronary arteries. The angiograms were reported independently by the radiologists, who were unaware of the results of other investigations. A significant lesion was defined as luminal narrowing in one or more of the major coronary arteries of ≥70% in magnitude. Left main stem stenosis was classed as two vessel disease. Five patients with normal coronary arteries had ergonovine provocation in which a mean dose of 0·6 mg was given intravenously and the angiograms were repeated.

Results

AMBULATORY ST SEGMENT MONITORING AND SEVERITY OF CORONARY ARTERY DISEASE

Of the 100 patients monitored, 58 developed 294 episodes of reversible ST segment changes during each 24 hour period of ambulatory monitoring. Five patients had no significant coronary artery disease at angiography, one had normal coronary arteries and localised spasm induced at angiography, and 52 had varying severity of coronary artery disease (Table 1). Fifty six patients developed episodes of reversible ST segment depression only, whereas two had episodes of ST segment depression and elevation. The number of episodes of ST segment change varied from 1 to 66 in a 48 hour period and the duration varied from 2 minutes to 16 hours 40 minutes. The maximum magnitude of ST segment depression varied between 1 and 5 mm and ST segment elevation between 1 and 6 mm.

ST SEGMENT CHANGES IN RELATION TO SEVERITY OF CORONARY ARTERY DISEASE

One patient with three vessel disease and one with normal coronary arteries and localised coronary spasm in the left circumflex coronary artery had episodes of ST segment elevation and depression during ambulatory monitoring. All other patients had episodes of ST segment depression only. The frequency and duration of episodes of ST segment change were generally greater in patients with more severe coronary artery disease (Table 1). Patients with no significant coronary artery disease or coronary spasm had 2 (1·6) episodes lasting 44 (57) minutes per 24 hours compared with patients with three vessel disease who had 7·3 (9·2) episodes of ST segment shift lasting 99 (119) minutes per day. These differences were, however, not statistically significant (Table 1, Fig. 1). Patients with more than six episodes of ST segment change in a day had two or three vessel disease or spasm with normal coronary arteries (Fig.1). Indeed, 20% of all patients with two or three vessel disease had more than six episodes of ST segment change during a 24 hour period. The duration of ST segment change and the maximum magnitude of ST segment depression also tended to increase with increasing severity of coronary artery disease (Table 1), but differences between the groups were not statistically significant. Seven patients with left main stem stenosis were studied. Six of these patients also had stenoses in the right coronary artery. The number of episodes and the duration of ST segment changes in

Table 1 *Frequency, duration, and magnitude of the episodes of ST segment change during ambulatory electrocardiographic monitoring in 100 patients with varying severity of coronary artery disease and nocturnal angina. Values are mean (SD)*

	Coronary artery disease						*Nocturnal angina*
	Not significant	*Spasm only*	*1 vessel*	*2 vessel*	*3 vessel*	*Left main stem stenosis*	
Total No of patients	25	1	22	22	30	7	12
With ST segment changes (%)	5 (19)	1	11 (50)	17 (77)	24 (80)	7 (100)	12 (100)
Total No of episodes	2 (1·6)	1·8	2·9 (1·9)	3·7 (4·4)	7·3 (9·2)	17 (13)	12 (8·6)
Duration of episodes	44 (57)	7 (4)	63 (52)	59 (73)	99 (119)	174 (65)	3·8 (1·6)
Mean maximum ST change (mm)	1·5 (0·5)	1·6 (0·5)	1·1 (0·3)	2·5 (1·1)	2·3 (1·5)	3·8 (1·6)	3·4 (1·4)

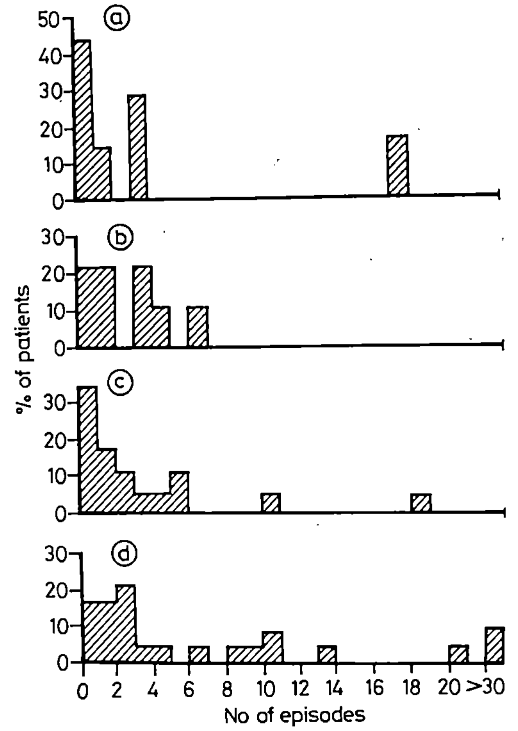

Fig. 1 *Frequency of transient ST segment changes (number of episodes) in patients with (a) no significant disease, (b) one vessel disease, (c) two vessel disease, and (d) three vessel disease.*

these patients tended to be greater than in any other group of patients (Table 1). Six of the seven patients with left main stem stenosis also had nocturnal ST segment changes.

NOCTURNAL ST SEGMENT CHANGES

Twelve patients with nocturnal ST segment changes were identified during ambulatory monitoring. A mean of 2·8 (1·8) episodes of ST segment shift occurred between midnight and 06.00 in this group of patients. These patients also had more frequent episodes of ST segment change (12 (8·6)) during the daytime when compared with any individual coronary artery disease group (Table 1). Nine patients had three vessel disease, two had two vessel disease, of whom one had left main stem stenosis, and only one had normal coronary arteries and confirmed coronary spasm. Both patients with episodes of ST segment elevation had nocturnal episodes. The duration and magnitude of the episodes of ST segment change in patients with nocturnal angina were also greater when compared with individual coronary artery disease groups (Table 1). All patients with coronary artery disease and nocturnal angina who were exercised had positive exercise tests at low workloads (Table 2). Seven patients developed significant ST segment depression within three minutes and three within six minutes of exercise (mean 2·8 (1·1) minutes) (Table 3).

HEART RATE RELATION TO ST SEGMENT CHANGES

The heart rate at the onset of the episodes of ST segment change was also measured (Table 3). There was a wide variation in the heart rate at the onset of ST segment depression between episodes in the same patient and also between patients with the similar severity of coronary artery disease. The mean heart rate before ST segment depression occurred tended to be higher (123 (10) beats/min) in the five patients with normal coronary arteries than in those patients with coronary artery disease (101 (12) beats/min) (NS). There was no significant difference between the mean heart rates at the onset of ST segment depression in patients with one, two, and three vessel disease (Table 3) (mean range 99–105 beats/min). Nevertheless, patients with left main stem stenosis and those with nocturnal angina tended to develop ischaemia at relatively lower mean heart rates of 89 and 91 beats/min (Table 3) respectively.

The distribution of the episodes of ST segment change during the day and night in patients with coronary artery disease was also investigated (Fig. 2). Most of the episodes of both painful and painfree ST segment changes occurred during the morning and early afternoon. Relatively fewer episodes occurred in the evening, and the fewest episodes occurred at night. The diurnal variation in the mean hourly heart rates in 15 patients with no significant coronary artery

Table 2 *Duration of exercise tests to 1 mm ST segment depression in patients with varying severity of coronary artery disease and nocturnal angina. Figures are numbers of patients*

Duration of exercise (mins)	*Coronary artery disease*						*Nocturnal angina*
	Not significant	*Spasm only*	*1 vessel*	*2 vessel*	*3 vessel*	*Left main stenosis*	
3	0	0	3	4	14	4	7
4–6	2	0	4	9	8	2	3
7–9	1	0	4	3	1	0	0
>9	2	0	2	1	0	0	0
Negative test	20	1	9	5	6	0	1

Table 3 *Heart rate at the onset of episodes of ST segment changes during ambulatory electrocardiographic monitoring in relation to the duration of exercise to and heart rate at the onset of 1 mm ST segment depression during exercise testing in patients with varying severity of coronary artery disease and nocturnal angina. Values are mean (SD)*

	Coronary artery disease						*Nocturnal angina*
	Not significant	*Spasm only*	*1 vessel*	*2 vessel*	*3 vessel*	*Left main stem stenosis*	
Total No of patients	26	1	22	22	30	7	12
			Ambulatory monitoring				
No with episodes (%)	5 (19)	1	11 (50)	17 (77)	24 (80)	7 (100)	12 (100)
Heart rate at onset of episodes (beats/min)	123 (10)	87 (10)	99 (16)	105 (13)	99 (14)	89 (14)	91 (13)
			Exercise testing				
Exercise duration to ST depression (mm)	9 (2·7) (n=6)	—	5·4 (2·5) (n=13)	5·5 (2·3) (n=16)	3·9 (1·8) (n=22)	2·6 (1·2) (n=6)	2·8 (1·1) (n=10)
Heart rate at 1 mm ST depression (beats/min)	136 (16) (n=6)	—	124 (25) (n=13)	114 (22) (n=16)	109 (19) (n=22)	99 (16) (n=6)	100 (10) (n=10)

—, negative

disease and 15 with frequent ST segment depression shows that the mean heart rate is higher during the morning and early afternoon compared with the evening and is lowest at night (Fig. 3).

COMPARISON WITH EXERCISE TESTING

Table 3 shows the mean duration of exercise before significant ST segment depression occurred in patients who had ST segment changes during ambulatory ST segment monitoring. The duration of exercise to significant (1 mm) ST segment depression was shorter in patients with more severe coronary artery disease (left main stem stenosis, nocturnal angina, and three vessel disease) compared with patients with less severe coronary disease. These differences were, however, not statistically significant.

The mean heart rate at the time of 1 mm ST segment depression tended to be higher in patients with no significant coronary artery disease (136 beats/min) when compared with patients with coronary artery disease (113 beats/min) (not statistically significant). Patients with relatively severe disease, left main stem stenosis and three vessel disease, had a lower heart rate threshold at which significant ST segment depression occurred during stress testing (Table 3). Patients who had a very low threshold to ST segment depression during the exercise tests had more frequent episodes of ST segment depression, which also lasted longer (Table 4); although the differences were not statistically significant. All 40 patients who developed 1 mm ST segment depression during the first six minutes of exercise had episodes of ST seg-

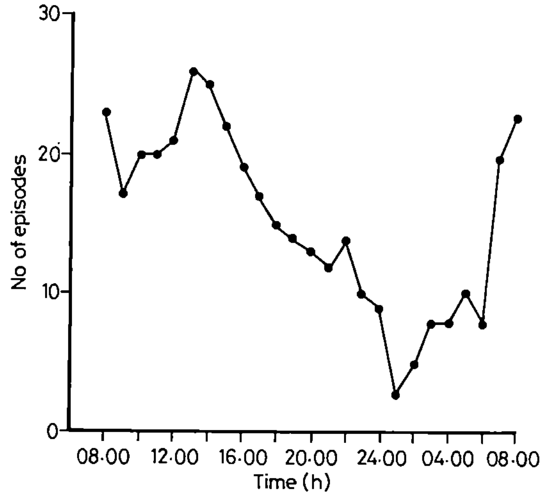

Fig. 2 *Diurnal variation in the number of episodes of transient ST segment change in 73 consecutive patients over 24 hours.*

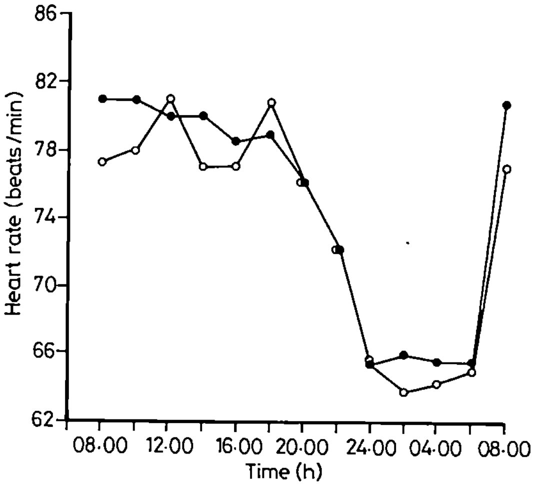

Fig. 3 *Diurnal variation in the mean hourly heart rate in 15 patients with normal coronary arteries (○) and 15 patients with frequent angina pectoris (●).*

Table 4 *Presence, frequency, and duration of ambulatory ST segment changes in patients with coronary artery disease (CAD) and positive exercise tests (1 mm ST segment depression)*

No of patients with CAD	20	20	8	2
Duration of exercise to 1 mm ST depression (min)	≤3	4–6	7–9	10–12
No of episodes of ST change	7·6 (8)	2·8 (2·2)	1 (1·3)	0
Duration of episodes (min)	132 (124)	38 (35)	33 (50)	0
No of patients with no ambulatory ST segment changes	0	0	2	2

ment change during ambulatory monitoring. In contrast, four patients with exercise tests becoming positive after nine minutes (stage III of the modified Bruce protocol) had no episodes during ambulatory ST segment monitoring (Table 4).

A majority of patients (86%) with a positive exercise test within three minutes of the modified Bruce protocol had two or three vessel coronary artery disease, but only 35% of patients with such disease had a positive test at this low workload (Table 2). Only seven of the 11 patients with frequent nocturnal ischaemia during ambulatory monitoring had an exercise test which was positive within three minutes and one had a negative exercise test. Whereas all the patients with left main stem stenosis who were exercised had a positive stress test, only four of the six developed significant ST segment depression within the first three minutes of exercise.

Discussion

Abundant laboratory and clinical evidence now exists to show that shifts in the ST segment on the electrocardiogram in patients with coronary artery disease represent episodes of myocardial ischaemia, whether or not these episodes are associated with pain.[16–18] Changes in the ST segment accompanying myocardial ischaemic events have been recorded under controlled conditions such as at rest or during exercise testing for many years. Ambulatory electrocardiographic ST segment changes have been capable of accurate and reliable recording and reproduction only since the advent of recorders with an adequate low frequency response[15] (0·05 Hz<3 db down). A few studies have been conducted to detect the occurrence of ST segment changes in patients with chest pain,[7 8 14] those with a positive exercise test,[12 13] and those with varying severity of coronary artery disease.[9 13] Nevertheless, none of these studies included consecutive patients, and the patients studied were highly selected. By studying consecutive admissions we have been able to determine the true incidence of daytime angina, nocturnal rest angina, and coronary artery spasm with normal coronary arteries in the population of patients referred to one hospital. This has enabled us to determine the implications of the varying frequency and duration of ST segment changes observed during ambulatory monitoring in relation to findings at coronary arteriography and during conventional exercise testing.

The results of monitoring 73 consecutive patients with significant coronary artery disease show that the number and duration of episodes of ST segment change increase with increasing severity of the underlying disease, but there is a substantial overlap between the groups. Myocardial ischaemia occurred more frequently during the daytime than during the evening and night (Fig. 2). The diurnal variation in the averaged hourly heart rate in 15 patients with the most frequent episodes of ST segment changes (Fig. 3) did not differ significantly from that in patients with normal coronary arteries. The close correlation between the basal heart rate changes and the frequency of myocardial ischaemia during the day and at night highlights the importance of underlying changes in metabolic demand in the development of myocardial ischaemia during daily life. This has been confirmed in a recent study comparing atenolol with pindolol in patients with angina pectoris.[19] Suppression of basal heart rate with the former drug reduced the ischaemic episodes significantly when compared with pindolol, which did not reduce basal heart rate as a result of intrinsic sympathomimetic activity.

The importance of heart rate changes at the onset of myocardial ischaemia has also been shown: the mean heart rate before the onset of ST segment depression was (101 (12) beats/min) higher than the basal heart rate during any time of the day or night (Fig. 3). By performing an analysis of momentary changes in the heart rate before the onset of ST segment depression, we have shown that there are invariably small but significant increases in heart rate before the onset of ST segment depression in patients with obstructive coronary artery disease.[20] It must be emphasised that different magnitude of increases in heart rate precede episodes of ST segment change in individual patients and in patients with similar severity of coronary artery disease. Although these findings indicate the importance of changes in metabolic demand in the precipitation of myocardial ischaemia, other possible factors such as increases in end diastolic pressures during recumbency and dynamic coronary stenosis cannot be entirely excluded.

The heart rate threshold before myocardial ischaemia occurred was lower in patients with more severe forms of coronary artery disease during stress testing (Table 3), a finding also reported in previous studies.[21] The heart rate at the onset of the episodes of ST segment change during ambulatory monitoring was similarly lower in patients with more severe disease such as left main stem stenosis. The mean heart rate at the onset of ST segment depression during ambulatory monitoring was 10–20 beats/min lower than the heart rate at which 1 mm ST segment depression occurred during exercise testing (Table 2). Measurement of the heart rate at the first change in the ST segment during exercise testing has not been performed and is certain to be lower; thus there seems to be a similarity in the mean heart rate threshold to ischaemia in both exercise testing and ambulatory monitoring, although there is often a large variation in individual patients.

Exertional angina is considered to be secondary to myocardial oxygen demand exceeding supply, whereas rest and nocturnal ischaemia is often considered to be secondary to coronary spasm.[22] Ambulatory electrocardiographic ST segment monitoring is unique in being able to identify non-invasively this group of patients with normal coronary arteries and coronary spasm. This is a rare condition and accounted for only one of the 26 patients with normal coronary arteries and one of the 12 patients with nocturnal angina pectoris. The other 11 patients with nocturnal angina had three vessel or left main coronary artery disease and a very low exercise threshold to ischaemia. Thus patients with severe coronary artery disease develop ischaemia even at rest, and coronary spasm in normal or near normal coronary arteries is a relatively rare cause of nocturnal angina.

Both exercise testing and ambulatory monitoring failed accurately to predict patients with normal coronary arteries. Six patients with no significant coronary artery disease had episodes of ST segment changes during ambulatory monitoring. Five of these patients also had false positive exercise tests. The other patient was shown to have coronary spasm induced at angiography but had a negative exercise test. The duration of exercise to ST segment depression and the heart rate at which ST segment depression occurred (136 (16) beats/min, range 120–155 beats/min) was much greater in patients with normal coronary arteries than in those with significant coronary artery disease (Table 3). Similarly, the heart rate at which ST segment depression occurred during ambulatory monitoring in these five patients (123 (10) beats/min, range 108–137 beats/min) also tended to be higher than in patients with significant coronary disease. False positive exercise tests with similar episodes of ST segment depression during ambulatory monitoring have been previously reported in young healthy volunteers.[23] The heart rate at which ST segment depression occurred in these healthy subjects was 135 (20) beats/min (range 100–180 beats/min), a rate similar to that of patients in this series with normal or near normal coronary arteries. Thus patients with normal coronary arteries developed ST depression at relatively high heart rates during both ambulatory monitoring and exercise testing.

Attempts have been made in the past to correlate the electrocardiographic changes during exercise testing with the long term prognosis in patients with ischaemic heart disease.[24] The patients with ST segment depression at low workload, those with a greater magnitude of ST segment depression, and those with exercise induced ventricular arrhythmias have a worse prognosis and also tend to have more severe forms of coronary artery disease. Information on the prognostic importance of ambulatory electrocardiographic ST segment changes is lacking. Nevertheless, it is widely known that patients with three vessel disease and left main stem coronary artery disease have a relatively poor long term prognosis. It would, therefore, be valuable to identify non-invasively this subgroup in a group presenting with chest pain. These results show that ambulatory ST segment monitoring detected transient episodes of ST segment changes in 80% of the patients with three vessel disease and in all patients with left main stem stenosis. Patients with more severe coronary artery disease also had more frequent episodes of ST segment changes during the day (Table 1). Indeed 11 of the 12 patients with nocturnal angina had either severe two or three vessel disease or left main stem stenosis. Exercise tests were also positive in 79% of the patients with three vessel disease, but the duration of exercise did not identify patients who had nocturnal ischaemia nor those with left main stenosis (Table 2). Mortality and morbidity in patients with three vessel coronary artery disease varies,[25] and those patients who have more frequent ischaemia may possibly have greater risk of infarction or death, although long term studies are required to substantiate this view.

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Predictive value of early maximal exercise test and thallium scintigraphy after successful percutaneous transluminal coronary angioplasty

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SUMMARY Restenosis of the dilated vessel after percutaneous transluminal coronary angioplasty can be detected by non-invasive procedures but their ability to predict later restenosis soon after a successful angioplasty as well as recurrence of angina has not been assessed. A maximal exercise test and myocardial thallium perfusion scintigraphy were, therefore, performed in 91 asymptomatic patients a median of 5 weeks after they had undergone a technically successful angioplasty. Primary success of the procedure was confirmed by the decrease in percentage diameter stenosis from 64(12)% to 30(13)% as measured from the coronary angiograms and in the trans-stenotic pressure gradient (normalised for mean aortic pressure) from 0·61(0·16) to 0·17(0·09). A clinical follow up examination (8·6(4·9) months later) was carried out in all patients and a late coronary angiogram obtained in 77. The thallium perfusion scintigram showing the presence or absence of a reversible defect was highly predictive for restenosis whereas the exercise test was not. The positive predictive value of an abnormal scintigram was 82% compared with 60% for the exercise test (ST segment depression/or angina or both at peak workload). Angina or a new myocardial infarction occurred in 60% of patients with abnormal and in 21% of patients with normal scintigrams.

Restenosis of the dilated vessel after primary successful percutaneous transluminal coronary angioplasty occurs in 19–33% of cases within the first six months after the procedure.[1–4] Changes in the dilated and non-dilated arteries may be detected by changes in the patient's clinical status, by non-invasive diagnostic tests, or by repeat coronary angiography. Previous work[2 5] has shown that an abnormal exercise test response and a myocardial perfusion deficit on thallium scintigrams was associated with an angiographically detected restenosis of the dilated vessel or with the presence of additional disease. The present study was performed to determine the value of early non-invasive testing for the prediction of restenosis and recurrence of symptoms. The patients included in this study had undergone a technically successful angioplasty and had remained free of angina pectoris at the time of the exercise test and thallium scintigraphy, which were performed a median of 5 weeks after the procedure. Follow up data on the recurrence of symptoms and a control coronary angiogram obtained a median of 7 months after the procedure were compared with the initial non-invasive test results.

Patients and methods

STUDY POPULATION

Of 265 consecutively attempted angioplasty procedures followed up for at least six months, 91 attempts in 87 patients (75 men, 12 women) were selected for this study. The inclusion criteria were (*a*) a primary successful angioplasty, (*b*) early maximal exercise testing combined with thallium myocardial perfusion scintigraphy, and (*c*) absence of anginal symptoms after the procedure until the time of non-invasive testing. A single stenosis was dilated in 89 cases and a double stenosis (left circumflex and anterior descending arteries) in two. Eight had previously undergone

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coronary artery bypass surgery. The dilated vessel was the left anterior descending artery in 61 patients, the left circumflex artery in nine, the right coronary artery in 18, and a saphenous vein bypass graft in three. Sixty seven patients had one vessel disease, 13 two vessel disease, and three three vessel disease. In the remaining eight, previous bypass surgery was performed with complete revascularisation as shown at angiography in four of them.

After angioplasty, a complete anatomical correction was obtained in 73 procedures, while additional disease not suitable for dilatation by us was still present in 18 cases. Seven of these 18 patients had unstable angina refractory to medical management. Angioplasty of the vessel thought responsible for the symptoms was attempted because the patients were not considered ideal candidates for surgery in view of associated disability or recent myocardial infarction. In the remaining 11 patients, the residual lesions not suitable for angioplasty were also not suitable for bypass surgery or reoperation.

ANGIOPLASTY

The procedure was performed according to the technique of Grüntzig *et al*,[1] using the equipment of Schneider via a femoral route. Details regarding the procedure used in our laboratory have been previously described.[6 7] The procedure was considered to be successful when the residual stenosis was$<50\%$ in diameter with a good runoff and filling of the distal vessel at angiography. In the 87 cases with satisfactory recordings, the residual pressure gradient (normalised for the mean aortic pressure) was$<0{\cdot}2$ in 57 cases and $<0{\cdot}4$ in 28.[8]

All patients received nifedipine 10 mg every two hours for the first 12 hours after the procedure and were maintained on salicylic acid 500 mg a day and nifedipine 10 mg 3–6 times a day until repeat angiography was performed. Beta blocking agents were withdrawn unless hypertension was present.

EXERCISE TEST AND MYOCARDIAL THALLIUM SCINTIGRAPHY

The non-invasive exercise studies were performed 5·2(2·5) weeks (mean (SD)) after the angioplasty. Before testing, a careful history was obtained and only patients free of typical angina were included. The subjects underwent a maximal or symptom limited exercise test on the bicycle ergometer with stepwise increments of 20 W every minute. Intravenous dipyridamole[9] was used as an alternative for the exercise test in four patients who were unable to cycle. The three orthogonal leads XYZ of the Frank lead system were monitored, processed, and analysed as previously described.[10] Horizontal ST depression $\geqslant 0{\cdot}1$ mV or typical angina during exercise were considered to be an abnormal (or positive) exercise test response. One minute before peak exercise, thallium 50 MBq (1·5 mCi) was injected intravenously and imaging started five minutes later in the anterior and left anterior oblique 45° and 65° views. Static planar images (500 kcounts full field) were obtained after exercise and four hours later. The late images were corrected for acquisition time differences with respect to the early images. After interpolative background correction[11] and automated left ventricular contour detection,[12] circumferential profiles were computed and compared with the normal range defined by the upper and lower tenth percentile at each point of the profile from 15 normal subjects. These methods used for data collection and processing have been described before.[12] The analogue images and the circumferential profiles were prospectively analysed on a consensus basis by three experienced observers without knowledge of the angiographic data. The segmental thallium uptake was scored both in the postexercise and late images on a four point scale, from normal (3) to absent (0). The scores of all segments were summed for each patient and the total difference between late and early postexercise scores was taken as a measure of the amount of redistribution. An increase in thallium uptake score of two points or more between postexercise and late images was taken as the cutoff between normal and abnormal scintigrams. Using this analysis, the previously reported sensitivity and specificity for the diagnosis of coronary artery disease were 80% and 88% respectively.[12]

ANGIOGRAPHIC FOLLOW UP AND QUANTITATIVE CORONARY ANGIOGRAPHY

A repeat coronary angiogram was requested in all 91 patients six months after the angioplasty and actually performed in 77. The interval from the procedure was 7·4(2·5) months in the patients who remained asymptomatic and 5·5(2·7) months in the patients who had recurring symptoms. Angiograms were obtained in multiple views (including hemiaxial views for the left coronary artery) and were interpreted by the angiographers without knowledge of the non-invasive test results. Restenosis was defined as an increase in the diameter stenosis of the dilated lesion to$>50\%$. In addition, quantitative analysis of the dilated stenosis was obtained in the same angiographic projection before and after angioplasty and at follow up by means of our computer based coronary angiographic analysis system.[7 13]

CLINICAL FOLLOW UP

The patients were followed up in the outpatient clinic until the occurrence of typical angina pectoris or a new myocardial infarction, or both, repeat angioplasty, or coronary artery bypass grafting. Clinical information was obtained in all 91 patients and the follow up duration was 8·6(4·9) months (mean (SD). No patient died during this period.

ANALYSIS OF RESULTS

Results are presented as mean (standard deviation). Paired or unpaired *t* tests were used whenever appropriate. The predictive value of a given test or of a combination of tests was calculated as the percentage of patients with an event among those who had that given test result. The influence of the extent of the thallium reversible defect on its predictive value was assessed by the Armitage test.[14]

Results

Table 1 gives details of the angioplasty procedure and of the exercise test for patients with restenosis of the dilated lesion (n=23), with long term successful angioplasty but additional disease (n=17), and with long term successful angioplasty and complete anatomical correction (n=37), and patients without angiographic follow up (n=14). Before angioplasty the mean percentage diameter stenosis was slightly less in those patients with primary successful dilatation and additional disease ($p<0·05$), but no significant difference between groups was observed after the procedure. At follow up, on average no further change was observed except, by definition, for those patients with restenosis (Fig. 1). There was no significant difference between groups in the pressure gradient across the stenosis either before or after the angioplasty. Similarly, the time of exercise testing after the procedure and the maximal workload and heart rate achieved were comparable in all groups.

Ninety six per cent of the patients who exercised reached 80% of their predicted maximal workload. An abnormal exercise test was found in 30 patients: 18 had ST segment depression, 10 angina at peak workload, and two both. Exercise induced ischaemia as assessed by the thallium redistribution was observed in 41 patients. During follow up, angina recurred in 34 patients and two had a new myocardial infarction in the territory of the dilated vessel (an inferior infarction due to right coronary artery occlusion two years after successful angioplasty of the left anterior descending coronary artery was also observed). Nine patients had a repeat angioplasty and three underwent coronary artery bypass surgery. Among these, one patient with a successful angioplasty at five months had unstable angina pectoris seven months later owing to progression of coronary artery disease in other vessels (Table 2).

PREDICTIVE VALUE OF TESTS

Figure 2a shows the predictive value of the noninvasive tests in the 77 patients with follow up angiograms. An abnormal thallium scan was associated with a high probability of restenosis or with the presence of additional disease; this probability was not influenced by the exercise test result (81% of restenosis when both tests were abnormal *vs* 83% when tests were discordant). Conversely, a normal thallium scan was associated with a low probability of restenosis or additional disease or both. This probability was also not influenced by the exercise test result

Table 1 *Angiographic findings before and after percutaneous transluminal coronary angioplasty (PTCA) and details of exercise testing according to four patient groups*

	Restenosis (n=23)	*Additional disease (n=17)*	*Long term success (n=37)*	*No control angiography (n=14)*
		Angiographic findings		
Dilated vessel:				
LAD	18	10	24	9
LCX	1	4	3	1
RCA	3	3	10	2
Bypass	1	—	—	2
% (Mean, SD) diameter stenosis:				
Before PTCA	67(14)	58(12)	65(11)	68(12)
After PTCA	32(13)	25(14)	31(12)	30(10)
At follow up	63(11)	30(12)	32(12)	—
Mean (SD) pressure gradient*				
Before PTCA	0·66(0·15) (n=22)	0·58(0·10) (n=16)	0·60(0·14) (n=36)	0·57(0·23) (n=14)
After PTCA	0·18(0·11) (n=23)	0·18(0·9) (n=15)	0·16(0·8) (n=8)	0·16(0·11) (n=13)
		Exercise test		
Mean (SD) No of weeks after PTCA (range)	5·3(2·6) (3–12)	5·2(2·1) (2–8)	4·9(1·8) (2–8)	5·6(2·4) (3–12)
Mean (SD) maximal workload (% of predicted)	93·2(15·3)	98·2(13·7)	90(16·5)	99·3(14·3)
Mean (SD) maximal heart rate (beats/min)	146(28)	147(27)	151(22)	146(23)

Translesional pressure gradient is normalised for the mean aortic pressure.
*LAD, left anterior descending, LCX, left circumflex, RCA, right coronary artery;
n, number of available measurements.

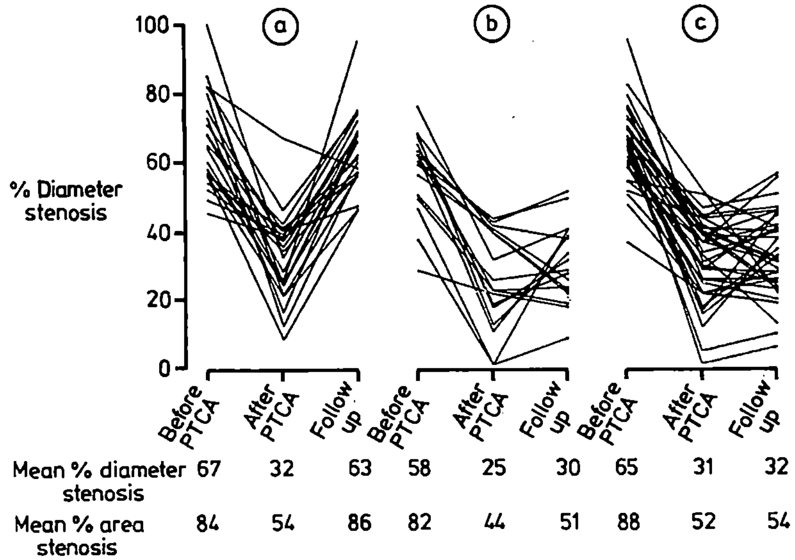

Fig. 1 *Percentage diameter of the dilated stenosis for patients with (a) restenosis (n=23), (b) additional disease (n=17), and (c) complete correction (n=37) as shown by quantitative angiography before and after angioplasty and at late follow up.*

(29% of restenosis when both tests were normal *vs* 22% when tests were discordant). Figure 2b shows similar findings in the subgroup of patients with complete anatomical correction after the angioplasty. The predictive value of an abnormal thallium scan was 74% whereas the probability of restenosis in patients with a normal thallium scan was 16%. Again, the exercise test result had no predictive value.

Figure 3 shows the value of the non-invasive tests results for the prediction of recurrence of angina or occurrence of a new myocardial infarction or both in all 91 patients. The probability of a later coronary event was 65% when both tests were abnormal and decreased to 52% when only the thallium scan was abnormal. In the presence of a normal thallium scan, the probability was low (about 20%) regardless of the result of the exercise test. The positive and negative predictive values were respectively 60% and 78% for thallium scintigraphy and 53% and 67% for the exercise test.

Table 3 shows the influence of the severity of ischaemia on the predictive value of the thallium scintigram. As far as the angiographic endpoint was concerned, the percentage of patients with restenosis or additional disease or both increased from 24 when no ischaemia was present to 75 when a slight degree of redistribution was observed ($p<0 \cdot 001$), which was even below the abnormality threshold used in this

Table 2 *Exercise test results and recurrence of symptoms during follow up in four patient groups*

	Restenosis (n=23)	*Additional disease (n=17)*	*Long term angiographic success (n=37)*	*No repeat angiography (n=14)*
Abnormal exercise test:				
Angina	1	3	6	—
ST depression	7	3	4	4
Both	—	1	—	1
Abnormal scintigram	17	11	6	7
Symptoms:				
Recurrent angina	16	8	6	4
New myocardial infarction	—	2	—	—
Treatment:				
Repeat angioplasty	7	2	—	—
Coronary artery bypass graft	1	1	1	—

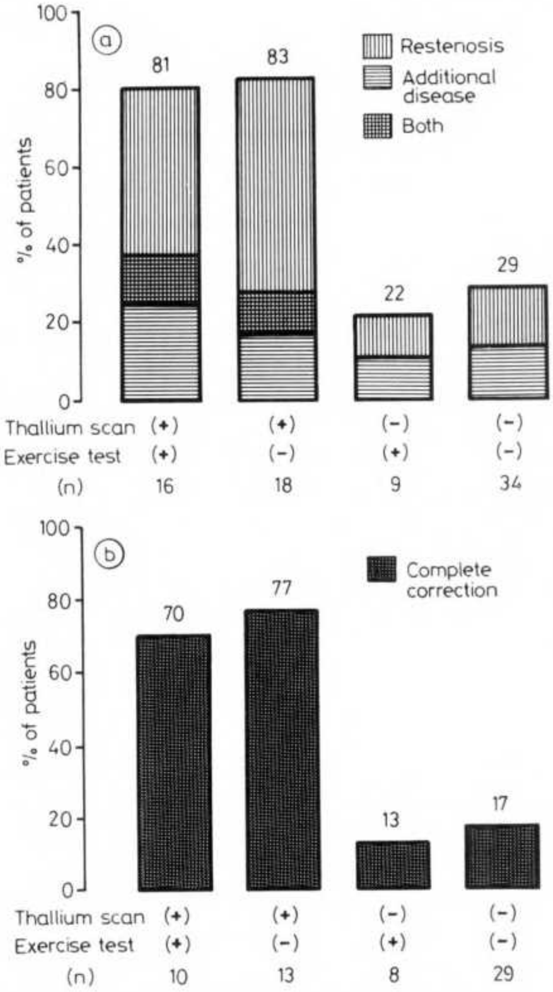

Fig. 2 *Predictive value for restenosis of the various possible combinations of non-invasive test results (a) in patients with restenosis or additional disease or both, and (b) in patients with complete correction after angioplasty (PTCA). n, number of patients; (+), abnormal test; (−), normal test.*

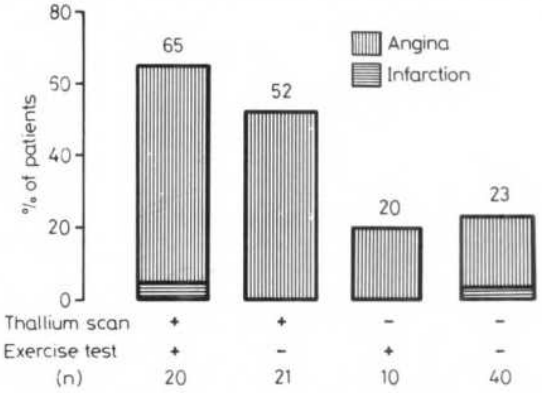

Fig. 3 *Predictive value for recurrence of angina or myocardial infarction or both of the non-invasive tests. n, number of patients; (+), abnormal test; (−), normal test.*

study. Further increase in the size or in the severity of the reversible thallium defect was not associated with an increased probability of significant restenosis at angiography. On the contrary, the percentage of patients who had a coronary event during the follow up period increased stepwise as the ischaemia became more severe (p=0·001).

Discussion

The present study shows that the early assessment of myocardial perfusion by exercise thallium-201 scintigraphy after a successful angioplasty has a high predictive value for restenosis and recurrence of angina during the follow up period. Since restenosis after the procedure is known to occur mainly during the first 4–6 months after the procedure,[2–4] the repeat coronary angiography was planned at six months unless angina recurred earlier. Furthermore, the duration of the clinical follow up (mean 8·6 months) was deliberately short since symptoms recurring after than period are more likely to be related to the progression of coronary artery disease rather than to restenosis of the initially dilated vessel.

Changes in the severity of the stenosis were assessed visually by the angiographers and objectively characterised in a single projection by a computer based analysis system. The mean percentage diameter stenosis for the entire group before angioplasty was 63%. This value is at least 10% lower than that which is commonly reported when eyeball readings of the angiograms are relied on.[15 16] Visual interpretation of diameter reductions is known to systematically overestimate the severity of the stenosis.[17] Moreover, lumen reductions of 90% are rarely suitable for angio-

Table 3 *Effect of the severity of ischaemia on the predictive value of thallium scintigraphy*

	*Redistribution score**			
	0	*1*	*2*	*>3*
% Restenosis or additional disease or both	24	75†	71	84
% Recurrence of angina or infarction or both	22	29†	50†	67†

*Difference in thallium uptake score from postexercise to late image; †$p<0·001$ (p represents the significance of each probability increment according to the severity of ischaemia).

plasty since such lesions, with an obstructed diameter of as little as 0·35 mm, are unlikely to be crossed even by a low profile deflated balloon catheter which has a mean diameter of 0·8 mm. As shown experimentally,[18] angioplasty induces non-axisymetric changes of the atherosclerotic lesions so that they can no longer be assessed from a single angiographic projection. Accordingly, the use of orthogonal or multiple projections has been recommended.[19] This was not a major limitation in this study since after angioplasty intrapatient changes were the main interest.

Previous studies using non-invasive tests to evaluate the results of angioplasty have focused on the reversibility of the ischaemic changes after a successful procedure and on their induction at the time of recurrence.[2 5 20 21] The ability of the non-invasive tests to predict restenosis and recurrence of angina has not been evaluated. The study from the Montreal group, however, reports observations similar to our findings[2]: among six asymptomatic patients who had persistently abnormal thallium scintigrams one month after angioplasty restenosis was present at six months in two (out of five) who had a control angiogram.

In the present study, the high predictive value of the perfusion scintigram contrasts with the poor predictive value of the exercise test, at least for the prediction of restenosis. This might be related to a lower sensitivity of the exercise test for the detection of moderate coronary narrowing compared with thallium scintigraphy. The combination of a normal exercise test with a reversible thallium perfusion abnormality could be an early indicator of the presence of a non-critical stenosis, still insufficient to induce ST segment depression during exercise.[22 23] Indeed, 60% of the patients with an initially abnormal scintigram became symptomatic during the follow up period. Thus the most likely explanation for our findings is that restenosis had already occurred to some extent at the time of non-invasive testing in the majority of patients in whom it was detected later. Pathological studies of the underlying mechanism of restenosis after dilatation support this hypothesis. Fibrocellular proliferation as a reparative response to coronary wall laceration has been found in necropsy studies[24] and may represent the pathological substrate of early restenosis. By analogy with aortic dissection, exposure of vascular smooth muscle cells to blood may trigger an exuberant tissue reaction leading to the obliteration of the false channel and eventually of the functional lumen. Data from experimental angioplasty in pigs suggest that balloon dilatation is a potent stimulus to early platelet deposition and subsequent intimal hyperplasia.[25] In this model, the reparative process was seen by two weeks after the procedure. That may have allowed the early detection of restenosis in our patients.

Another possible explanation for our findings may be that the abnormal scintigrams occurred predominantly in patients in whom the dilatation was incomplete. This seems unlikely to us since only successful cases were included and the decrease in the severity of the stenosis and in the trans-stenotic pressure gradients was comparable in patients with restenosis and sustained angiographic success. Because of a selection bias, restenosis of the dilated artery occurred in 30% of the patients who had a control angiogram, while angina pectoris recurred in 40% of all patients. These results do not represent the true incidence of restenosis at our institution since the availability of a thallium scintigram was a requirement for inclusion in this study. The high incidence of recurrent angina must also be related to the inclusion of patients with disease in additional vessels in whom dilatation, although successful, did not result in complete anatomical correction. Hence, an obligatory long term relief of symptoms could not be expected. Angina recurred in 61% (11 out of 18) of these patients.

The clinical implications of these findings for the routine management of patients undergoing angioplasty remain to be elucidated. Certainly an abnormal stress thallium scintigram early after the procedure in an asymptomatic patient is an indication for close clinical monitoring in view of the high chance of the recurrence of symptoms. Currently, we consider that decisions to perform a control angiogram, followed by a redilatation when restenosis is found, should primarily be based on the severity of the anginal symptoms rather than on the results of the testing procedure by itself. This is analogous to the issue of bypass surgery for documented coronary artery disease in asymptomatic patients, particularly now that no benefit of surgical intervention over pharmacological treatment was found in mildly symptomatic or asymptomatic patients.[26] As long as the outcome of prophylactic angioplasty has not been studied, the procedural complications and incomplete success rates would militate against carrying out angioplasty when diagnostic testing shows restenosis in the absence of symptoms.

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Randomised placebo controlled trial of aspirin and dipyridamole in the prevention of coronary vein graft occlusion

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SUMMARY Treatment with the combination of aspirin and dipyridamole is believed to reduce the incidence of coronary vein graft occlusion. A double blind randomised controlled trial was carried out in which aspirin 990 mg and dipyridamole 225 mg daily or placebo were added to the routine postoperative managment (warfarin for three months) of 320 patients undergoing coronary bypass grafting. The trial treatment was given for 12 months, after which the results were assessed by coronary and graft angiography. The two randomised groups, each of 160 patients, were comparable in age, sex, symptomatic state, angiographic findings, and operative procedure. Repeat coronary arteriography was carried out on 266 patients, 133 in each group. All grafts and distal anastomoses were patent in 68% (91/133) of the placebo patients and in 75% (100/133) of those receiving active treatment. Overall graft patency was 87% (306/352) and 89% (342/385) respectively. Retrospective subgroup analysis showed patency rates of 72% (26/36) and 78% (39/50) of grafts to vessels requiring preliminary endarterectomy, and 80% (36/45) and 91% (40/44) of distal anastomoses to vessels measured at operation to have a diameter of ≤1 mm. None of these differences was significant at the 5% level.

Thus in this group of patients with high graft patency rates, treatment with aspirin and dipyridamole conferred no appreciable advantage.

One of the main causes of recurrent or persistent angina after an aortocoronary bypass operation is graft occlusion.[1–3] This complication, whether it occurs early from thrombosis or later from progressive subintimal proliferation,[4 5] is believed to result from perioperative endothelial damage followed by deposition of platelets on to the subendothelial tissues,[6] and, in the experimental animal, its occurrence can be limited by treatment with the combination of aspirin and dipyridamole.[7 8] Moreover, this combination has been shown to decrease lipid accumulation in the intima of vein grafts implanted into the arterial circulation of both normolipaemic and hyperlipaemic monkeys.[9] Several clinical trials of platelet inhibitor and anticoagulant treatment have been reported,[10–19] but the findings have been conflicting and in many instances do not withstand critical scrutiny.[20] We report a randomised placebo controlled trial in which we assessed the effect of the combination of aspirin and dipyridamole on coronary vein graft patency one year after operation. The treatment was added to our routine management with conventional anticoagulation for the first three months and was started in the early postoperative period.

Patients and methods

SELECTION OF PATIENTS

Consecutive patients of either sex up to the age of 70 years, who had undergone coronary arteriography and had been referred for aortocoronary bypass grafting, were considered for entry into the trial. Patients were excluded for the following reasons: (*a*) previous coronary bypass operation; (*b*) coexistent valvar heart

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disease; (*c*) history of peptic ulceration, hiatus hernia, or indigestion; (*d*) known intolerance to aspirin or dipyridamole; (*e*) habitual use of aspirin or other anti-inflammatory drugs; (*f*) recognised indication for antiplatelet treatment (for example, transient cerebral ischaemic attacks) or the need for anticoagulant treatment which was likely to extend beyond three months after operation; (*g*) significant bleeding disorder or reduced platelet count; (*h*) any condition which might increase the risk of elective coronary and graft angiography (for example, cerebrovascular disease); (*i*) more than four months between coronary arteriography and surgery; and (*j*) refusal to take part.

The purpose and potential risks of the trial were explained to each patient, and signed consent was obtained. The protocol was approved by the ethics committee of the National Heart and Chest Hospitals.

RANDOMISATION

Patients were randomised in equal numbers to the placebo or active treatment groups. Whenever possible the long saphenous vein was used for the bypass grafts, but when this was unsuitable another vein from the leg or arm vein was used. After its removal, and before implantation, the vein was kept in heparinised blood. The internal mammary artery was not used routinely for bypass grafting but when, in occasional patients, this technique seemed most appropriate such grafts were excluded from the analysis. The size of the grafted arteries was measured with a probe; vessels of ≤ 1 mm diameter were considered to be small. The presence of disease at the site of the distal anastomosis and the performance of endarterectomy were also recorded. The distal anastomoses were constructed with continuous 6/0 or 7/0 prolene and were carried out according to the preference of the individual surgeon, either with the heart fibrillating and the temperature allowed to drift to 28°C or with the heart arrested by cold cardioplegia.

Our original intention had been to start the trial treatment as soon as the patient had given his consent and to continue it up to the night before operation. The fourth patient, however, died during his operation mainly as a result of severe bleeding. The operation had been technically difficult and prolonged, but he had been taking the active treatment; thereafter the capsules were started on the second or third postoperative day as soon as the chest drains had been removed and the patient was able to take tablets by mouth. The medication was packaged and labelled for double blind administration and each capsule contained either placebo or aspirin 330 mg plus dipyridamole 75 mg and was given three times daily. At the same time treatment was started with warfarin and this was continued, maintaining the prothrombin time between two and three times control (British Comparative Thromboplastin), for the first three months. Administration of the trial capsules was continued until the patient's readmission for assessment by graft and coronary angiography after one year. Patients were asked not to take additional aspirin, dipyridamole, sulphinpyrazone, or other anti-inflammatory drugs during this period, and paracetamol was recommended for mild pain.

COMPLIANCE

Compliance with the prescribed treatment was assessed by questioning the patient and by a urine test for aspirin at the first postoperative outpatient visit (usually eight weeks after operation).

DATA ANALYSIS AND STATISTICS

The grafts were characterised as patent or occluded. Grafts with multiple distal anastomoses (sequential grafts) were considered both in terms of the patency of each anastomosis and of the graft itself. The data were analysed on the "intention to treat" principle, and the two groups were compared by their overall graft patency rate and by the proportion of patients with all grafts patent. Based on a consecutive series of patients who were reinvestigated during 1975–76 after aortocoronary bypass grafting at the London Chest Hospital, in which the graft patency after one year of treatment with warfarin for the first three months was 83% and the mean number of grafts was 2·5 per patient, we estimated that the inclusion of 150 patients would give a 90% probability of detecting a 50% reduction in graft occlusion rate. To allow for withdrawals from the trial and to increase its power while limiting the recruitment period we decided to enroll 300 patients, and this figure was subsequently increased to 320 with the realisation that the placebo patency rate was likely to be higher than had been expected.

In addition, the influence of treatment on the disease in segments of bypassed arteries which were proximal to the distal vein graft anastomosis was assessed by comparing the preoperative and postoperative angiographic appearances of bypassed vessels which, on the first angiogram, were patent between their origin from the aorta and the site of the subsequent anastomosis. The disease was defined as having progressed if the artery was occluded on the second angiogram; no attempt was made to assess lesser degrees of progression.

Angiography was carried out and analysed without knowledge of the patient's randomisation. The code was broken for an individual patient only when there was a medical requirement to know whether he had been receiving active treatment; any decision to withdraw the trial capsules was made on the assumption that active treatment was being given. A preliminary analysis was made after the entry of 200 patients, and it was at this stage that the high placebo group vein graft patency was discovered and the decision to increase the recruitment to 320 patients was taken.

Results

During the recruitment period from 11 October 1978 to 3 October 1982 a total of 1054 patients had a primary isolated coronary artery bypass operation carried out at the London Chest Hospital. Seven hundred and thirty four patients were excluded from the trial, 400 (54%) because their angiogram was more than four months old, 23% because of known intolerance to aspirin, a previous history of peptic ulceration, hiatus hernia, or indigestion, and 10% because they refused to take part. The remaining 17% were too old, lived abroad, required regular anti-inflammatory drugs, were considered unsuitable for elective reinvestigation, or were omitted for administrative reasons.

Three hundred and twenty patients agreed to take part and were randomised, 160 to receive placebo and 160 to receive active treatment. There were no significant differences between the two groups in age, sex, the severity of their symptoms, coronary disease and left ventricular function, or in the number of grafts subsequently implanted. There were similar numbers of cigarette smokers and patients with hypertension and hyperlipidaemia but over twice as many diabetic patients ($p<0{\cdot}05$, χ^2 test) in the active than in the placebo group (Table). Three patients died preoperatively, and two refused operation after randomisation, so that 315 (156 in the placebo group and 159 in the active group) actually underwent aortocoronary bypass grafting. Seven patients (six in the active group, one in the placebo group) died in the perioperative period before starting the trial medication. One patient in the active group, as mentioned previously, who was pretreated, also died perioperatively. There were five late deaths, two in the active and three in the placebo group.

COMPLICATIONS

The trial capsules were withdrawn from 35 patients after the development of complications or symptoms which were suspected of having been caused by aspirin. Minor gastrointestinal disturbances, such as abdominal discomfort, heartburn, nausea, or vomiting, occurred in 18 patients receiving active treatment and in 10 of those receiving placebo. Two patients, one from each group, developed uncomplicated duodenal ulcers. Life threatening complications occurred in five patients: three receiving active treatment had severe gastrointestinal haemorrhages within the first two weeks, while one placebo group patient had a perforated duodenal ulcer one week postoperatively and another a severe gastrointestinal haemorrhage after two months. Eight additonal active group patients reported minor side effects but continued to take the trial treatment. The difference in frequency of side effects between the two groups is statistically significant ($p<0{\cdot}01$, χ^2 test).

In the active group there was a marginally significant decline in haemoglobin concentration between the initial and final assessments ($p<0{\cdot}05$, paired t test; measured decrease 0·39 g/dl), and haemoglobin concentrations were higher in the placebo group than in the active group at the final evaluation ($p<0{\cdot}01$, t test).

COMPLIANCE

In the placebo group 123 (77%) patients took the trial capsules substantially as instructed, whereas in the active group 116 (73%) complied with the treatment. Of the patients who underwent coronary and graft angiography after one year, the compliance rates were 87% and 83% respectively.

Thirty six patients (19 in the placebo and 17 in the active group) who were alive one year after their operations either withdrew from the trial or were not recatheterised because of medical reasons which might have increased the risk of complications from the procedure.

CORONARY AND GRAFT ANGIOGRAPHY

Repeat coronary arteriography was carried out on 266 patients, 133 in each group. The mean time to reinvestigation after surgery was 12·4 (SD 1·7) months in the active group, and 12·2 (SD 2·1) months in the placebo group. In all but six cases the graft or a distinct stump were selectively catheterised. One graft which was not entered was seen to be patent on an aortogram; the others (two in the placebo and three in the active group) were assumed to be occluded. In two placebo group patients there was uncertainty about the patency of one anastomosis of a sequential graft; both were designated as occluded.

In the placebo group there was a total of 352 vein grafts (including 16 sequential grafts) with 369 distal anastomoses (mean 2·8/patient). There were three internal mammary grafts. Vein graft patency was 87% (306/352) and distal anastomosis patency 86% (318/369). Endarterectomy was carried out on 36 arteries, and the grafts to 26 (72%) of these vessels were patent. All the grafts were patent in 72% (96/133) of the patients and all the distal anastomoses in 68% (91/133).

In the active group 360 vein grafts (including 24 sequential grafts) were implanted with 385 distal anastomoses (mean 2·9/patient) and two internal mammary grafts. Vein graft (321/360) and distal anas-

Table *Characteristics of patients receiving either placebo or active treatment. Figures are numbers (%) of patients unless stated otherwise*

	Placebo	*Active*
No of patients randomised	160	160
Men/women	143/17	139/21
Age (range) (yr)	54·5 (26–70)	54·2 (33–69)
Hypertension (>160/90 mm Hg)	35 (22)	32 (20)
Diabetes	6 (4)	15 (9)
Serum cholesterol concentration (mmol/l)	7·13 (SD 1·35)	7·16 (SD 1·4)
Serum triglyceride concentration (mmol/l)	2·30 (SD 1·82)	2·30 (SD 1·67)
Smoking (>10 cigarettes/day):		
Preoperatively	71 (44)	81 (51)
Postoperatively	22 (14)	26 (17)
Peripheral vascular disease	12 (7)	9 (6)
Angina grade*:		
0	6 (4)	4 (3)
1	6 (4)	1 (0)
2	46 (29)	57 (36)
3	43 (27)	33 (21)
4	59 (37)	65 (41)
Previous myocardial infarctions:		
0	73 (46)	73 (46)
1	64 (40)	71 (44)
2	17 (11)	14 (9)
>2	6 (4)	2 (1)
Electrocardiogram:		
Normal	47 (29)	50 (31)
Abnormal	113 (71)	110 (69)
No of coronary arteries with >75% stenosis (LMS)†:		
1	42	31
2	58 (2)	54 (6)
3	60 (7)	75 (7)
Left ventricle—No of abnormal segments ‡:		
0	48 (30)	50 (31)
1	74 (46)	67 (42)
2	30 (19)	35 (22)
3	8 (5)	8 (5)
Operation—No of distal vein graft anastomoses:		
1	10 (6)	7 (4)
2	43 (28)	36 (23)
3	81 (52)	79 (50)
>3	22 (14)	36 (23)
No of arteries endarterectomised	36 (10)	50 (13)
No of arteries of <1 mm diameter (% of distal anastomoses)	45 (12)	44 (11)

*0, no angina; 1–3, mild, moderate, severe, effort angina; 4, rest angina.

†No of principal arterial systems—that is, left anterior descending, right coronary artery or dominant atrioventricular circumflex, or circumflex.

‡Left ventricular free wall divided into three segments on right anterior oblique angiogram.

LMS, left main stem.

tomosis (342/385) patency were 89%. Endarterectomy was performed on 50 vessels with a subsequent graft patency of 78% (39/50). All the grafts and distal anastomoses were patent in 75% (100/133) of the patients.

To examine the possibility that active treatment might confer particular benefit to grafts implanted into small coronary arteries an analysis was made of the patency rates of grafts to vessels measured at the time of operation to have a diameter of ≤1 mm. Patency was 80% (36/45) in the placebo group and 91% (40/44) in the active group. Similarly, the two groups were compared in terms of patency of grafts to vessels in which there was disease at the site of the distal anastomosis but in which endarterectomy had not been carried out; the patency rates were 92% (68/74) for the placebo group and 93% (67/72) for the active group.

In the placebo group 28% (74/261) of bypassed arteries which were patent preoperatively had progressed to occlusion compared with 25% (68/271) in the active group.

In none of these comparisons was the difference between the two groups statistically significant at the 5% level, though in all cases there was a trend in favour of active treatment.

Discussion

Analysis of the factors which are known to influence the natural history of coronary heart disease and the results of bypass grafting indicates that the two randomised groups were well matched, though the excess of diabetes in the active group might have affected their results adversely in comparison with the placebo patients. There were, however, sources of potential bias which must be discussed.

Firstly, only 30% of the patients who underwent isolated coronary bypass grafting were entered into the trial. Those operated on more than four months after coronary angiography were excluded, and for much of the recruitment period the surgical waiting list was about six months in duration. The reason for this somewhat arbitrary time limit was our interest in the influence of treatment on progression of disease in the proximal segments of bypassed arteries; its effect was that a higher proportion of patients in the trial had been referred for early or urgent surgery compared with the overall coronary surgical practice at the London Chest Hospital. This is reflected in the high proportion with rest pain, the fact that three patients died before operation, and probably the high operative mortality of 3%. There is no obvious mechanism, however, by which this or any other of the exclusion criteria should have led to bias in favour of one group over the other or should preclude extrapolation of the results to other patients undergoing coronary vein bypass operations. A second problem arises from the patients who did not complete the trial protocol. The one year graft and coronary angiogram was not carried out on an equal number of patients in each group, though more of those in the active group had died (the majority before the trial medication was started), and of the survivors there was a higher proportion of women than among those who completed the trial protocol. Speculation on the influence of these incompletely investigated patients would be scientifically dubious, but since they comprised only 17% of the study group and, apart from the sex difference, their baseline characteristics were similar to those who completed the protocol no major bias should have been introduced.[20]

At the end of the first postoperative year the active treatment group had a higher proportion of patent grafts and a higher proportion of patients with all their grafts patent than the placebo group. Further analysis showed that almost all the difference is accounted for by grafts to small arteries and to those in which preliminary endarterectomy had been carried out: patency rates of grafts to vessels which were >1 mm in diameter and did not require endarterectomy were 89% in the placebo group and 90% in the active group. For none of these observations, however, are the observed differences statistically significant, and such subgroup analysis in a trial designed to examine overall graft patency is scientifically questionable. The results indicate, therefore, either that active treatment confers no benefit additional to that, if any, from routine anticoagulation or that a real benefit exists but is too small to have been detected by a trial of this size. In previous trials of platelet inhibitor treatment started in the postoperative period a trend in favour of active treatment has also been seen, though in only two of them was the observed advantage statistically significant: treatment with sulphinpyrazone was associated with a highly significant improvement in vein graft patency between one and two weeks postoperatively,[14] and in a trial of aspirin 1·3 g plus dipyridamole 100 mg daily graft patency was 15% higher in treated than in control patients six months after operation.[11] The second of these trials, however, was neither placebo controlled nor double blind, and only 65% of the patients were reinvestigated. Two trials of combined anticoagulant and antiplatelet treatment have been reported. Dale *et al* randomised 116 patients undergoing coronary bypass grafting to receive either aspirin 1 g plus warfarin daily or to act as an untreated control group.[18] At a mean period of 21 months after operation there was no overall statistically significant advantage from active treatment, but, of grafts which had peroperative flow rates of <50 ml/min, 76·2% in the treated group and 48·4% in the control group were patent. Harjola *et al* combined dipyridamole with warfarin and compared the results retrospectively with a group of patients managed with warfarin alone.[19] The warfarin group were restudied after about a year and the combined group after about two years. Graft patency was very much higher (95·7% *vs* 88·6%) in the combined treatment group, but a large number of internal mammary grafts was implanted and so the results do not necessarily compare with trials in which vein was used as the conduit.

As a result of experimental work which showed that platelet deposition begins as soon as the vein graft is implanted, Chesebro and Fuster argued that the optimal effect from platelet inhibitor treatment could be obtained only by starting treatment before operation.[20] This belief is strongly supported by the results of their own trial carried out at the Mayo Clinic[16 17] the design of which differed from the present study in only two important respects: firstly, dipyridamole was given preoperatively with aspirin added postoperatively, and, secondly, none of the patients were treated by conventional anticoagulation. Vein graft patency was very much higher in the active treatment group than in the placebo group, both early (up to six months, median 7 days), and one year after operation; moreover, active treatment slowed the rate of graft attrition during the first year. It should be noted, however, that the one year vein graft patency in the active group was the same as that in the present trial (89%), and that the large difference between the two groups at one year in the Mayo Clinic study is, therefore, a reflection of the lower placebo graft patency rate of 75%. Similarly, 78% of patients receiving active treatment in the Mayo Clinic trial had all their grafts patent at the end of the first year compared with the 75% reported here, whereas only 53%

of the placebo treated patients had this favourable outcome compared with the 72% in the present study. In other words, the conflicting results of the two trials are associated with a striking difference in the incidence of graft occlusion in their placebo patients. While this might be caused by differences in the patients or in operative technique, a more likely explanation is that warfarin treatment for three months had a beneficial effect in our placebo group and thereby diminished a true advantage conferred by aspirin and dipyridamole to the observed non-significant level. We included warfarin treatment in both groups for its assumed prevention of peripheral venous thromboembolism; the regimen adopted was the same as that used in our unit during the previous five years and the 4% higher graft patency in the placebo group of the present study could be ascribed to a combination of chance and to the greater surgical expertise which has been acquired since our earlier experience, on which the statistical projections were based. When the present trial was designed there was no evidence to suggest that anticoagulant treatment might have a favourable influence on vein graft patency, but three investigations have since been reported: one showed clear benefit,[12] one a non-significant trend,[13] and another, though carried out on a small number of patients, no benefit.[10]

The optimal dose of aspirin for the prevention of thrombosis in patients with vascular disease is controversial, and a low dose regimen has been recommended in the belief that this will inhibit platelet throboxane production but preserve prostacyclin synthesis in the vascular endothelium. This notion had not gained widespread acceptance at the time that the present trial was planned, and our dosage schedule was based on the augmentation by high dose aspirin of the dipyridamole effect on platelet survival time which has been shown both in patients with vascular disease[21] and in those with prosthetic heart valves.[22]

Thus the place of treatment with aspirin and dipyridamole of patients who have undergone coronary bypass grafting remains uncertain, though from consideration of the results of this trial in the context of others it seems likely that such treatment does retard the process of coronary vein graft occlusion and that the effect can be optimised by starting treatment with dipyridamole before operation. The present trial suggests, however, that this regimen has little advantage over that of conventional anticoagulation for three months, particularly for patients with technically satisfactory grafts to good sized coronary arteries. In our experience the anticoagulant regimen has been generally preferable to the administration of aspirin, which was felt to be contraindicated in a large number of patients and which, despite careful exclusion of those thought to be at risk, was accompanied by a high incidence of side effects. Our results do, however, lead us to agree that the aspirin-warfarin combination exposed patients to a considerable risk from haemorrhage,[23] which was not offset by the possible small overall benefit. The main problem, however, is that of the high risk grafts to vessels requiring preliminary endarterectomy or to those of small calibre. The advantage we observed from active treatment in these circumstances would, if real, be clinically valuable; the uncertainty can be resolved, however, only by further studies.

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Are the clinical benefits of oral prenalterol in ischaemic heart failure due to beta blockade?

A six month randomised double blind comparison with placebo

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SUMMARY The clinical effects of the oral beta_1 partial agonist, prenalterol, were investigated in 37 patients (29 male, eight female; mean age 57 years) with chronic ischaemic left ventricular failure using a placebo controlled randomised double blind protocol over six months. All patients were limited by dyspnoea (New York Heart Association class III) despite treatment with digoxin and diuretics. Twenty eight patients completed the protocol. Moderate clinical improvement was seen in the prenalterol group, whereas there was little change in the placebo group. Bicycle exercise capacity increased over six months in the prenalterol and placebo groups but only achieved statistical significance for prenalterol when compared with baseline values. Maximum exercise heart rate was significantly reduced in the prenalterol group compared with placebo. Radionuclide left ventricular ejection fraction at rest and during exercise and cardiothoracic ratio showed no significant improvement in either group over six months. Prenalterol was well tolerated and produced no increase in frequency of angina or ventricular arrhythmias.

Prenalterol produced clinical benefits and improved exercise tolerance while reducing exercise heart rate. A moderate placebo response was noted. The apparent beta blocking effect of prenalterol may be as important as the beta_1 agonist effect in producing these benefits. Prenalterol has, however, been withdrawn because of side effects in animals.

The management of patients with chronic ischaemic left ventricular failure is often difficult and unsatisfactory and usually requires multiple drug treatment.[1] The prognosis is poor despite treatment.[2] The conventional management is with diuretics and cardiac glycosides,[1] and, although the role of cardiac glycosides remains controversial,[3 4] recent studies have confirmed that some inotropic support is maintained in patients in sinus rhythm,[5–7] especially those with an audible third heart sound.[8] In the past decade there has been increasing interest in both vasodilator treatment[9 10] and inotropic drugs, particularly amrinone[11] and beta agonists.

The role of beta agonists in the management of heart failure has recently been reviewed.[12 13] The beta_2 agonists salbutamol and pirbuterol produce beneficial effects mainly by vasodilatation.[14] At present, there are apparently only two orally active selective beta_1 partial agonists: prenalterol and xamoterol [Corwin] (maximum agonist activity is 80%[15] and 43%[16] of that of isoprenaline respectively). Both drugs exert a positive inotropic effect acutely[16 17] and during short term maintenance treatment.[18 19] There is, however, a need for long term placebo controlled studies of these drugs in the management of left ventricular failure.[13] The occurrence of side effect in animals has led to the withdrawal of prenalterol, but our studies may be of more general interest.

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Table 1 *Patient characteristics. Figures are numbers of patients unless stated otherwise*

	Prenalterol	*Placebo*
No of patients	19	18
Male/female	13/6	16/2
Mean (SD) (yr)	57 (6·8)	57 (7·3)
Mean (SD) weight (kg)	66 (10·0)	71 (11·5)
Mean (SD) ejection fraction	0·27 (0·119)	0·26 (0·076)
Mean (SD) duration of left ventricular failure (yr)	2 (2·2)	2 (1·3)
Previous myocardial infarction	18	14
NYHA class III	19	18
Angina present	7	7
Atrial fibrillation	4	3
Mean (SD) dose (mg):		
Digoxin	0·25 (0·079)	0·23 (0·050)
Frusemide	107 (65·9)	120 (54·8)
Antianginal treatment	7	7

No statistically significant differences prenalterol *vs* placebo.

In this study the clinical effects of the beta$_1$ partial agonist prenalterol were assessed using a placebo controlled double blind protocol of six months' duration in patients with stable chronic ischaemic left ventricular failure.

Patients and methods

STUDY POPULATION

Patients were recruited during routine outpatient practice at three centres (Birmingham, Edinburgh, and Cambridge). A total of 37 patients entered the study (29 men, eight women), aged from 41 to 70 years (mean (SD) 57(7) years). All the patients were selected on the basis of having chronic left ventricular failure (duration >3 months) secondary to ischaemic heart disease and exercise tolerance limited by dyspnoea (New York Heart Association functional class III) despite treatment with digoxin and diuretics. Patients were excluded from the study if they had sustained a myocardial infarction within the previous three months, had valvar heart disease, or obstructive airways disease.

Table 1 summarises the patient characteristics. The presence of coronary artery disease was confirmed in all patients: in 23 by coronary angiography (18 of whom had a previous myocardial infarction) and in the remaining 14 by documented transmural myocardial infarction. Seven patients in each group were receiving antianginal treatment in the form of isosorbide dinitrate (20–90 mg/day) or nifedipine (30–

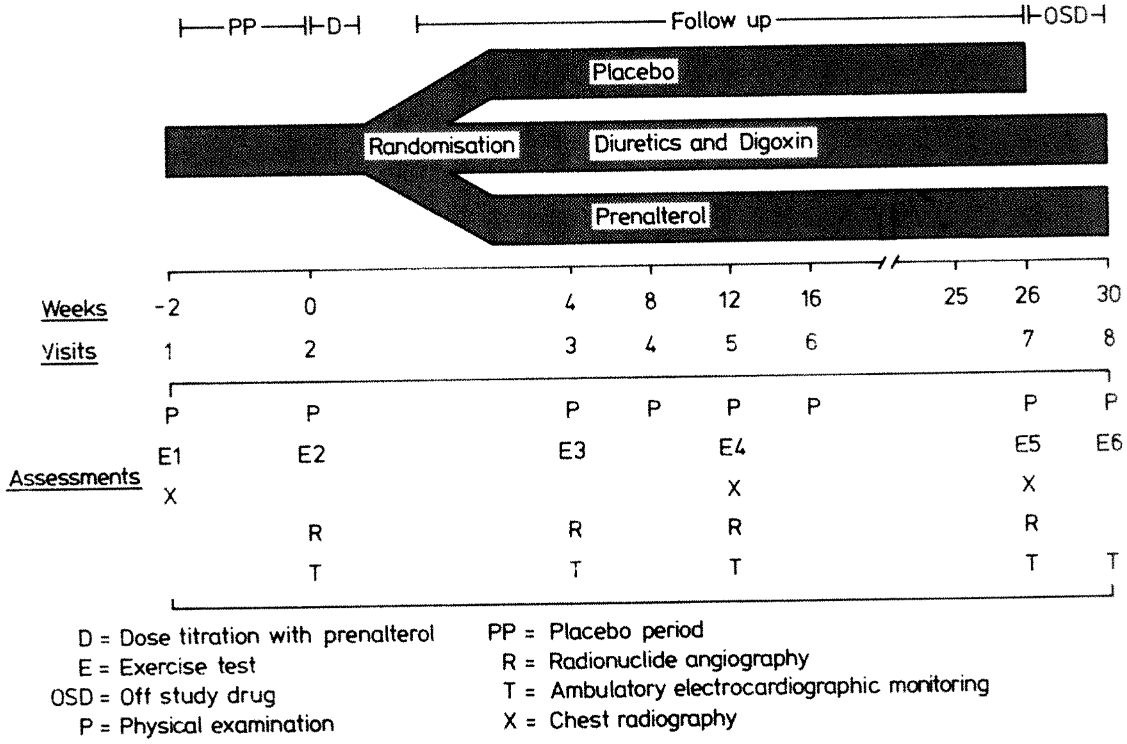

Fig. 1 *Study protocol.*

60 mg/day) or both, which was maintained throughout the study.

STUDY DESIGN

Figure 1 shows the study design. It consisted of a two week single blind placebo period followed by a single blind dose titration period. Oral prenalterol (prenalterol hydrocholoride controlled release tablets: AB Hassle) was given in incremental doses of 20 mg, 30 mg, and 50 mg at two-hourly intervals. The optimal dose was judged to be that which resulted in a moderate increase in resting heart rate of not more than 10 beats/min, with or without a rise in systolic blood pressure of not more than 20 mm Hg, and which could be tolerated without unwanted effects. Patients were then randomised to receive the optimal dose of prenalterol or matching placebo for six months. At the end of this period the treatment was withdrawn in a double blind fashion and a final assessment made one month later. The assessments were performed at the same time of day and at the same time after tablet administration in each patient. The doses of digoxin, diuretics, and other medication were kept constant throughout the study except where clinical deterioration necessitated alteration.

The protocol for this study was accepted by the United Kingdom Committee on Safety of Medicines under the Clinical Trial Certificate (CTC) scheme. The local ethical committees approved the study, which was performed according to the principles of the World Health Association's Declaration of Helsinki. Written consent was obtained from each patient.

Methods

TRIAL PROCEDURE

Clinical assessments—At each visit the patient and examining physician independently were asked to assess progress from the previous visit on a scale 1 to 7: 1, markedly worse; 2, moderately worse; 3, slightly worse; 4, about the same; 5, slightly improved; 6, moderately improved; 7, markedly improved. The patient's subjective score (based on symptoms) and the physician's objective score (based on physical signs) were then combined to give an overall clinical score. The baseline clinical score was taken to be 8 (4+4) in every case and at each visit the score increased or decreased in a cumulative fashion depending on the degree of changes from the previous visit. The patient's NYHA functional classification was also estimated by the physician.

Exercise tests—Maximal symptom limited exercise tests were performed on an electrically braked upright bicycle ergometer using a protocol which commenced at 20 W for two minutes and subsequently increased by 10 W per minute. The patient's heart rate and rhythm were continuously monitored and the heart rate and systolic blood pressure recorded at the end of each workload. Blood pressure was measured using a standard mercury sphygmomanometer.

Radionuclide angiography—Radionuclide angiography was performed following in vivo red cell labelling with 740 MBq technetium 99 m. Image data were aquired using a mobile gammacamera in the anterior and left anterior oblique projections at rest and the left anterior oblique projection during supine dynamic exercise. Count dependent global left ventricular ejection fraction was calculated from the background corrected time-activity curves from resting and exercise left anterior oblique images. Exercise was performed supine using an electrically braked bicycle ergometer. A single step protocol was used with a work level approximately 50% of the erect maximal level previously determined. A total of four minutes supine exercise was performed with image data acquisition during the last three minutes.

Chest radiography—A standard posteroanterior chest *x* ray film was taken at six feet for determination of the cardiothoracic ratio.

Ambulatory electrocardiographic monitoring—Standard 24 hour single channel recordings were made using an Oxford Medical Series 4.24 portable cassette recorder (Oxford Electronic Instruments, Oxford). Analysis of the recordings was carried out using a Pathfinder Mark II (Reynolds Medical Instruments) by a single operator. The results were reported using the Lown grading system.[20]

Haematological and biochemical analyses—Blood samples for routine haematological and biochemical tests and samples for subsequent plasma prenalterol[21] and digoxin assay were taken at the time of each clinical assessment.

Unwanted effects—Any unwanted effects were recorded at the time of each clinical assessment.

STATISTICAL ANALYSIS

All results are expressed as mean (standard deviation). Baseline values for resting and exercise heart rate and blood pressure were calculated as the mean of the two pretreatment measurements, whereas for radionuclide angiography and chest radiography the single pretreatment value was used. Student's t test for unpaired data was used to compare the differences in the baseline values and changes from baseline between the two groups, while a Student's paired t test was used to test the significance of the change from baseline within each treatment group. A Wilcoxon sum of ranks test was used to compare the cumulative clinical score between the two treatment groups.

Results

Nineteen patients were randomised to receive prenalterol and 18 to receive placebo. The patients were well matched at entry with no significant differences between the treatment groups (Table 1).

Table 2 *Number of deaths and withdrawals*

	Prenalterol (n=19)	*Placebo (n=18)*
Reason for death:		
Sudden cardiac death	1	2
Progressive severe cardiac failure with Mobitz type II heart block	1	0
Total	2	2
Events leading to withdrawal:		
Progressive cardiac failure	1	0
Acute myocardial infarction	1	0
Increased angina pectoris	0	2
Acute onset diabetes mellitus	0	1
Total	2	3

No statistically significant differences prenalterol *vs* placebo.

The optimal doses of prenalterol determined by dose titration were as follows: 100 mg twice daily, 17 patients (16 male, one female); 50 mg twice daily, 15 patients (nine male, six female); and 20 mg twice daily, 5 patients (four male, one female).

DEATHS, WITHDRAWALS, AND PROTOCOL VIOLATIONS

Two patients in each group died during the study, and two patients taking prenalterol and three placebo were withdrawn from the study (Table 2). During the study period the dose of diuretic (frusemide) had to be increased in two patients, from 80 mg to 160 mg/day in one case and from 80 mg to 240 mg/day in the other, because of deteriorating heart failure. Both patients were in the placebo group.

Table 3 *Results of assessments made throughout the trial. Values are mean (SD) (figures in square parentheses are numbers of patients)*

Treatment group	*At entry*	*During treatment*			*With no treatment*
		1 month	*3 months*	*6 months*	
Heart rate (beats/min)					
Prenalterol	83 (11·4) [19]	84 (12·1) [19]	82 (8·3) [15]	82 (10·3) [15]	82 (12·9) [14]
Placebo	87 (14·3) [15]	83 (12·4) [15]	88 (10·5) [13]	87 (10·8) [13]	89 (11·4) [13]
Systolic blood pressure (mm Hg)					
Prenalterol	126 (19·5) [19]	124 (22·1) [19]	118 (17·2) [15]	124 (19·9) [15]	123 (14·7) [14]
Placebo	117 (13·0) [15]	118 (14·4) [15]	115 (17·1) [13]	115 (15·4) [13]	111 (17·1) [13]
Diastolic blood pressure (mm Hg)					
Prenalterol	80 (10·7) [19]	78 (12·0) [19]	75 (12·3) [15]	76 (11·4) [15]	75 (7·3) [14]
Placebo	75 (6·9) [15]	78 (10·5) [15]	76 (13·7) [13]	75 (10·0) [13]	71 (13·4) [13]
Body weight (kg)					
Prenalterol	66·5 (9·41) [19]	67·2 (10·20) [19]	68·4 (11·63) [15]	70·2 (10·08) [14]	68·1 (8·11) [12]
Placebo	68·7 (11·04) [15]	69·4 (11·75) [15]	67·8 (12·50) [13]	68·0 (13·57) [12]	68·5 (13·01) [13]
NYHA classification					
Prenalterol	2·9 (0·27) [19]	2·7 (0·67) [19]	2·6 (0·74) [15]	2·6 (0·63) [15]	2·8 (0·58) [14]
Placebo	3·0 (0·13) [15]	2·9 (0·52) [15]	2·8 (0·44) [13]	3·0 (0·71) [13]	2·9 (0·76) [13]
Radionuclide ejection fraction at rest					
Prenalterol	0·27 (0·119) [15]	0·30 (0·150) [14]*	0·27 (0·135) [12]	0·27 (0·117) [13]	—
Placebo	0·26 (0·076) [12]	0·21 (0·092) [12]	0·24 (0·093) [9]	0·25 (0·095) [11]	—
Heart rate at rest (beats/min)					
Prenalterol	82 (14·5) [14]	83 (14·0) [13]	84 (9·8) [12]	82 (13·5) [11]	—
Placebo	85 (10·3) [10]	86 (13·0) [10]	83 (12·3) [9]	80 (8·0) [8]	—
Radionuclide ejection fraction during exercise					
Prenalterol	0·23 (0·120) [13]	0·25 (0·161) [12]	0·22 (0·110) [11]	0·23 (0·130) [10]	—
Placebo	0·24 (0·077) [9]	0·20 (0·092) [8]	0·22 (0·095) [9]	0·23 (0·068) [8]	—
Heart rate during exercise (beats/min)					
Prenalterol	122 (18·5) [12]	112 (12·8) [11]*	107 (12·5) [11]*	107 (11·6) [10]	—
Placebo	120 (10·0) [8]	117 (19·9) [9]	117 (22·1) [9]	112 (12·6) [8]	—
Cardiothoracic ratio					
Prenalterol	0·55 (0·069) [15]	—	0·54 (0·069) [16]	0·54 (0·066) [16]	—
Placebo	0·52 (0·038) [14]	—	0·52 (0·055) [14]	0·53 (0·051) [13]	—
Holter Lown score					
Prenalterol	2·4 (1·64) [15]	1·6 (0·63) [16]	2·2 (1·39) [13]	2·2 (1·05) [14]	2·5 (1·58) [8]
Placebo	2·9 (1·57) [14]	1·8 (0·99) [12]	2·5 (1·37) [13]	2·2 (1·03) [12]	3·2 (1·31) [8]
Plasma prenalterol concentrations (nmol/l of plasma)					
Prenalterol	—	193 (132·5) [15]	190 (152·4) [13]	116 (98·6) [12]	—
Placebo	—	0	0	0	—
Plasma digoxin concentrations (nmol/l of plasma)					
Prenalterol	1·9 (0·80) [12]	2·1 (1·65) [13]	2·3 (1·44) [11]	2·0 (1·30) [11]	—
Placebo	1·9 (0·91) [8]	2·1 (1·20) [8]	2·1 (1·18) [8]	1·8 (1·26) [9]	—

*p<0·05 between the treatment groups.

RESTING OBSERVATIONS

Table 3 shows resting heart rate and blood pressures. There were no significant differences between the groups before or during the study.

CLINICAL SCORES AND NYHA CLASSIFICATION

Figure 2 summarises the clinical scores. In the prenalterol group the increase in clinical scores corresponds to moderate improvement at three and six months. Fourteen of the 19 patients showed a positive clinical response with an increased score. In the placebo group the increase in clinical score corresponds to slight improvement, with 10 of the 18 patients having a small increase in score. The standard deviations (SD) for this group were large in contrast to the prenalterol group, which is a reflection of the variability in clinical response in the placebo group. Statistical significance (Wilcoxon test) was not reached for the differences in cumulative clinical score between the prenalterol and placebo groups.

The NYHA classification (Table 3) showed a trend in favour of the prenalterol group which was not statistically significant.

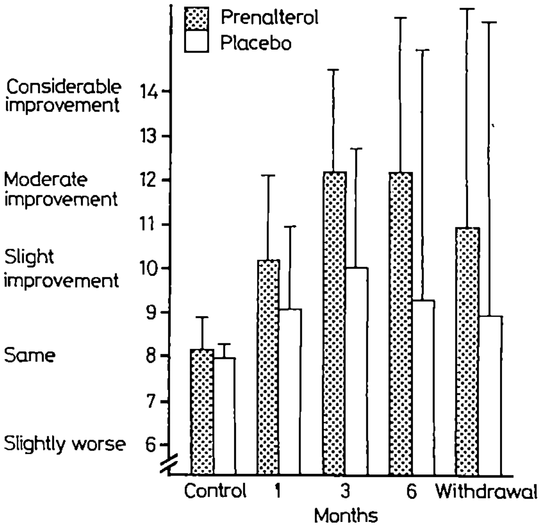

Fig. 2 *Mean clinical scores for patients treated with prenalterol or placebo. Bars denote SD.*

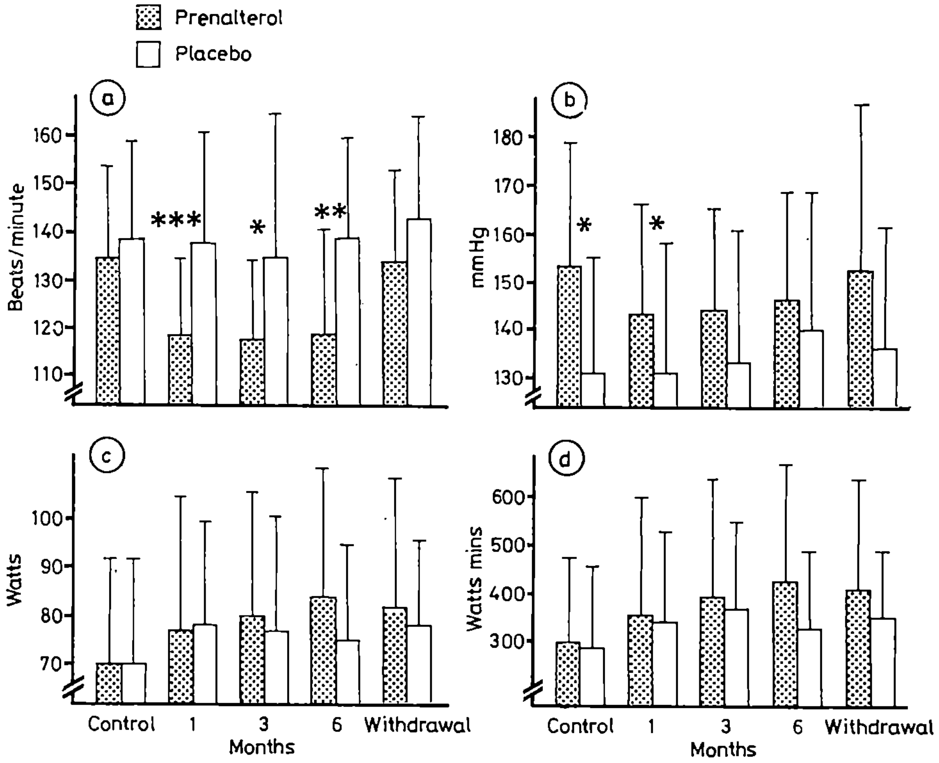

Fig. 3 *Maximal exercise test results for patients treated with prenalterol or placebo: (a) maximum heart rate; (b) systolic blood pressure at end of exercise; (c) maximum workload; and (d) total work. Values are mean (SD).* $^*p<0{\cdot}05$; $^{**}p<0{\cdot}01$; $^{***}p<0{\cdot}001$ *(between groups).*

EXERCISE TESTS

The exercise tests were performed without incident. The limiting symptom was breathlessness or fatigue or both in all cases throughout the study. Figure 3 shows the results.

Maximum heart rate was significantly reduced in the prenalterol group at one month ($p<0.001$), three months ($p<0.05$), and six months ($p<0.01$) compared with placebo. On drug withdrawal there was a return to control values.

During the control period systolic blood pressure at the end of exercise was significantly higher in the prenalterol group than in the placebo group ($p<0.05$). There was a tendency for the systolic blood pressure to be reduced in the prenalterol group during the treatment period, and this change reached statistical significance compared with placebo after one month ($p<0.05$). There was little change in the placebo values.

Rate pressure products were calculated from the above data and were found to be significantly reduced in the prenalterol group at one month ($p<0.001$), three months ($p<0.05$), and six months ($p<0.01$) compared with placebo.

The maximum workload (watts) achieved by the prenalterol group was significantly increased at one month ($p<0.05$) and six months ($p<0.01$) compared with control values. There was a significant increase in the placebo group at one month ($p<0.05$), but there were no significant differences between the treatment groups. On drug withdrawal there was no significant change in maximum workload achieved in either group.

The total work performed (watts mins) by the prenalterol group was significantly increased at one month ($p<0.05$) and at six months ($p<0.01$) compared with control values. In the placebo group there was a significant improvement at one month ($p<0.05$) compared with control values, but this was not maintained. There were, however, no significant differences between the groups.

RADIONUCLIDE ANGIOGRAPHY AND CHEST RADIOGRAPHY

Seven of the patients were in atrial fibrillation and were not studied. Table 3 shows the radionuclide left ventricular ejection fractions at rest and during exercise. There were no significant changes in the resting or exercise ejection fractions within the treatment groups during the study. Nevertheless, the differences between the groups for resting values alone at one month achieved statistical significance ($p<0.05$). The heart rate during supine exercise was significantly reduced in the prenalterol group compared with placebo at one and three months ($p<0.05$) (Table 3).

There was little change (NS) in the cardiothoracic ratio in both groups during the study (Table 3).

AMBULATORY ELECTROCARDIOGRAPHIC MONITORING

Cardiac arrhythmias were often recorded in the absence of symptoms in both groups at entry and during the trial period. Nevertheless, there was no significant difference in the occurrence of ventricular arrhythmias (Lown score) during the trial between the treatment groups (Table 3).

HAEMATOLOGICAL AND BIOCHEMICAL ANALYSES

No significant changes were observed in any of the standard haematological or biochemical analyses during the study period. In particular, there were no changes in serum glucose, potassium, or creatinine concentrations. Plasma digoxin and prenalterol concentrations confirmed drug compliance in all patients (Table 3).

UNWANTED EFFECTS

Table 4 shows the unwanted effects reported by patients. There was little difference in the incidence of unwanted effects between the groups. Four patients in each treatment group had the dose of study drug reduced because of unwanted effects. Digoxin was reduced in one patient in the placebo group and isosorbide dinitrate in one patient on prenalterol with good effect.

Table 4 *Unwanted effects*

Effects	*Prenalterol*	*Placebo*
Cardiac:		
Increased angina pectoris	3	5
Palpitations	3	1
Gastrointestinal:		
Heartburn	2	0
Nausea	1	3
Epigastric pain	1	1
Flatulence	1	1
Central nervous system:		
Headache	2	1
Insomnia	1	0
Tiredness	1	1
Depression	1	0
Allergic reactions:		
Itchy eyes	1	0
Other:		
Flushing	1	0
Tinnitus	1	0
Bizarre dreams	1	0

No statistically significant differences prenalterol *vs* placebo.

Discussion

In this study long term oral prenalterol treatment has been shown to be clinically beneficial, tending to improve symptoms and exercise tolerance in patients with chronic ischaemic left ventricular failure. These benefits appear to have occurred in the absence of any detectable improvement in left ventricular performance and were associated with a heart rate sparing effect during exercise. We also noted pronounced placebo response.

The selective beta_1 agonist, prenalterol, has been shown to have a significant positive inotropic effect when given intravenously,[22–25] and recently the inotropic effect has been confirmed during an acute oral dose-response study,[17] and during a short term oral double blind crossover study against placebo.[18] These changes have occurred in the absence of alterations in left ventricular preload and afterload. The improvement in exercise capacity which we found provides some indirect evidence of a positive inotropic effect, which was not detected by radionuclide angiography. Small changes in left ventricular ejection fraction are difficult to detect in patients with dilated poorly contracting hearts but could be of clinical importance. The lack of correlation between exercise capacity and left ventricular ejection fraction has been well documented in patients with left ventricular failure,[26 27] and compensatory mechanisms have been suggested to explain this.[28]

Chronic treatment with beta agonists could possibly produce tachyphylaxis owing to activation of the renin-angiotensin system[29] and "down regulation" of beta receptors.[30] It is interesting that we did not observe such tachyphylaxis. There was a small but insignificant weight gain in the prenalterol group. Nevertheless, none of these patients developed oedema or other symptoms of fluid retention, and we have attributed this increase in weight gain to the improved appetite and general well being observed during prenalterol treatment. Another possible disadvantage of beta stimulation is induction of cardiac arrhythmias and angina. We found no evidence that ventricular arrhythmias increased in the prenalterol group, and only two patients were withdrawn from the study because of increasing angina; both were taking placebo.

The attenuation in heart rate on maximal and submaximal exercise could have been the main way in which benefit was produced.[31] This attenuation was similar to that observed with conventional beta blocker treatment, even in patients with cardiac failure.[32] This leads us to propose that prenalterol reduces exercise heart rate by partial beta blockade. Consequently, the theoretical disadvantage of a full beta agonist—namely, increased myocardial oxygen demand—would be prevented. Indeed analysis of the rate-pressure product which approximates to myocardial oxygen consumption[33] is in keeping with this view. It may also explain our observation that the incidence of angina was not increased and that few arrhythmias were encountered. The finding that prenalterol did not depress left ventricular performance supports the fact that it is not a full beta blocker.[32]

The observed clinical improvement in 10 patients in the placebo group warrants further comment. This was perhaps due to the extra interest shown in the patients. They were severely limited by symptoms despite maximal conventional treatment and consequently were grateful for any hope offered by trial treatment. Compliance in such patients is usually excellent and was confirmed in this study.

Our study was designed to determine whether prenalterol produced improvement in exercise tolerance in patients with severe resistant heart failure. This assessment was used as an objective way of determining quality of life. The results show a definite trend towards improvement. The fact that evidence of improvement in left ventricular performance was lacking does not detract from the results.

Two placebo controlled studies have recently reported that prenalterol was of little benefit.[34 35] Why are our findings different? In both of these studies several of the patients had cardiomyopathy with normal coronary arteries or left ventricular failure of unknown origin, and some of the patients were in NYHA class IV. In contrast, all our patients had left ventricular failure of ischaemic origin and class IV patients were specifically excluded so that we studied a more homogenous group of patients. Additionally, the greater number of patients in our study may have enabled us to observe changes not apparent in the small groups of Lambertz (n=16)[34] and Currie (n=6).[35] The dose of prenalterol used in the Lambertz study[34] was lower than that which we used with resulting serum concentrations approximately half of those we obtained. In Currie's study[35] the treatment period was short so that it would have missed the clinical benefits which became apparent in our study after three months' treatment.

In conclusion, we found that prenalterol was well tolerated and no serious unwanted effects were observed. It appeared to be tolerated well in patients with angina as well as dyspnoea. The chronic effect of this partial beta_1 agonist on the myocardial beta_1 receptors and on the circulating endogenous catecholamines should be investigated to further elucidate its mode of action. Partial beta_1 agonist treatment appears to be of benefit in patients with ischaemic failure who are symptomatic despite maximal conventional treatment.

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Left ventricular volume and ejection fraction determined by gated blood pool emission tomography

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SUMMARY Electrocardiogram gated single photon emission computed tomography of the intracardiac blood pools is a recent development that involves the acquisition of images in multiple projections after in vivo erythrocyte labelling with technetium-99m and reconstruction of these images into tomographic sections in any desired plane. The technique was used in 25 subjects to measure left ventricular volume, by summing the areas of the ventricle in each of the tomographic sections, and the results compared with those using a counts based (non-geometric) technique from planar radionuclide ventriculography. Endocardium was defined with the aid of a contour at 43% of maximum left ventricular counts, and this contour was validated for a left ventricular phantom. Correlation between tomographic and counts based left ventricular volume was close. Similarly, ejection fraction correlated well. The technique is therefore an accurate method for determining left ventricular volume and ejection fraction, avoiding the assumptions about shape made by other geometric methods.

The size of the cardiac shadow on a chest *x* ray film is one of the most commonly used indices of cardiac function since it reflects principally the volume of the cardiac chambers. Because of the complex geometry of the heart, however, it is difficult to determine these volumes accurately. The recent development of the technique of electrocardiogram gated blood pool single photon emission computed tomography provides a geometric method for determining left ventricular volume, making no assumptions about the shape of the ventricle, and therefore promises to provide an accurate, relatively non-invasive measurement of left ventricular volume. The purpose of this study was to establish the place of the technique by comparison with a counts based radionuclide method for volume determination.

Patients and methods

GATED BLOOD POOL EMISSION TOMOGRAPHY

After in vivo erythrocyte labelling with 740 MBq (20 mCi) of technetium-99m sodium pertechnetate, the intracardiac blood pools were imaged using an IGE 400 Autotune ZS rotating gammacamera and Star computer. Thirty two views were acquired rotating from right anterior oblique through left anterior oblique to left posterior oblique, and each view was acquired for one minute. Within each view two frames were acquired by electrocardiogram gating, at end diastole and at end systole, and each frame was 100 ms duration. The time of end systole was determined from a planar radionuclide ventriculogram as described below. The two sets of planar images were reconstructed into end diastolic and end systolic transaxial sections by back projection using a Ramp-Hamming filter with cutoff frequency 0·5,[1] and from these, oblique sections orthogonal to the long axis of the left ventricle were constructed. Figure 1 shows the planes of the oblique sections. This protocol typically acquired 3 million counts in the end diastolic planar images, of which 65 000 were in the left ventricle. Left ventricular volume was determined from those horizontal long axis sections that contained part of the ventricle (typically eight sections), and in these left ventricular endocardium was defined manually with the aid of a contour at 43% of maximum counts within the whole ventricle. The sum of the

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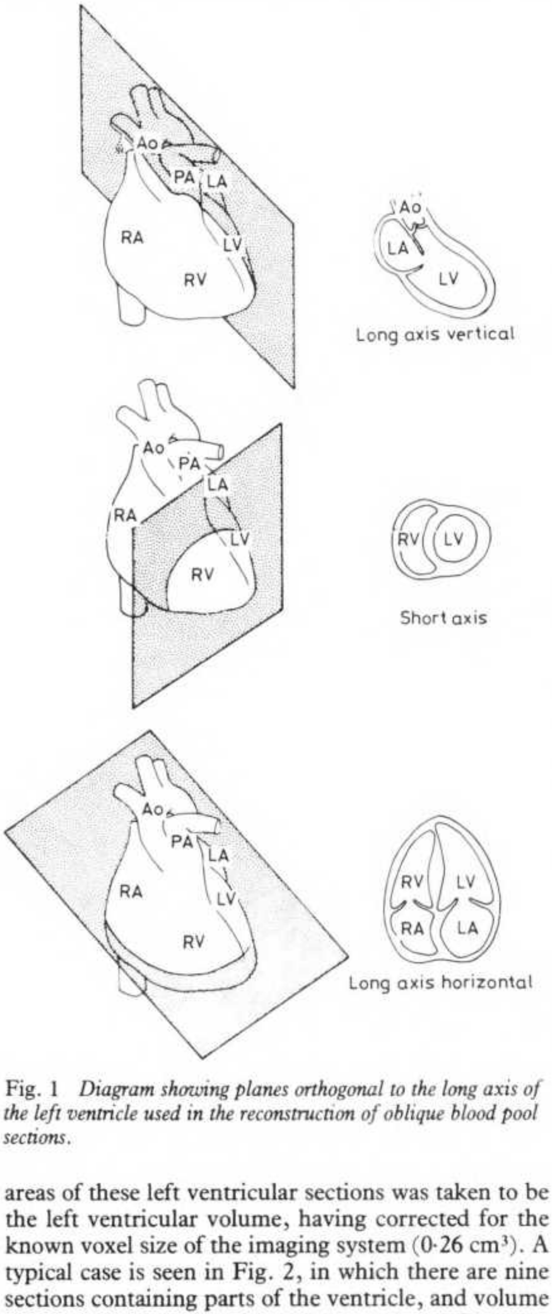

Fig. 1 *Diagram showing planes orthogonal to the long axis of the left ventricle used in the reconstruction of oblique blood pool sections.*

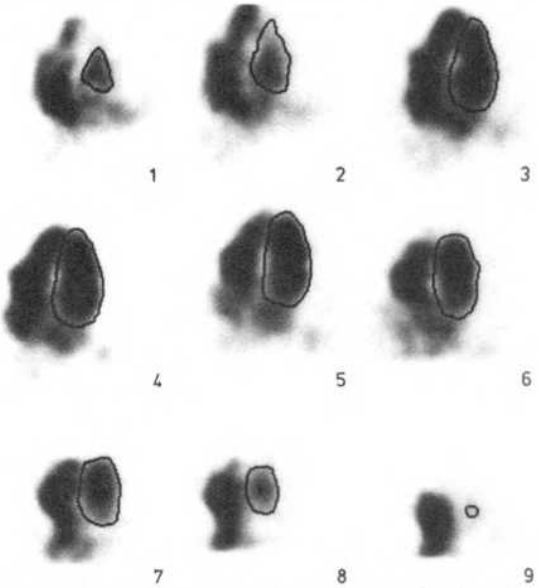

Fig. 2 *Nine horizontal long axis sections at end diastole cutting the left ventricle from inferior (1) to anterior (9) walls. The contours drawn define the left ventricular cavity, and volume is calculated from the sum of these areas (in this case 168 ml).*

areas of these left ventricular sections was taken to be the left ventricular volume, having corrected for the known voxel size of the imaging system (0·26 cm^3). A typical case is seen in Fig. 2, in which there are nine sections containing parts of the ventricle, and volume is calculated from the sum of the regions of interest shown.

PLANAR RADIONUCLIDE VENTRICULOGRAPHY

Planar equilibrium radionuclide ventriculography was performed in the left anterior oblique projection that best visualised the interventricular septum, and in addition 20° of caudal tilt were applied to minimise overlap between the left atrium and ventricle. Twenty four frames per cardiac cycle were acquired with electrocardiogram gating, and acquisition was for five minutes, providing approximately the same number of counts within the left ventricle at end diastole as for the tomographic study. Left ventricular volume was determined by an adaptation of the method of Links *et al*[2] as follows. Immediately after the acquisition a skin marker was placed over the centre of the left ventricular image, and another image was acquired at right angles (left posterior oblique) in order to measure the depth of the left ventricle. A 10 ml sample of blood was also taken and counted under the camera to determine the specific activity of the blood. After smoothing and background subtraction, left ventricular volume could be determined from the number of counts within the left ventricle using the specific activity of the blood and the depth of the left ventricle and assuming a linear attenuation coefficient of 0·10 cm^{-1}.[3]

PHANTOM STUDIES

To assess the accuracy of the different methods of volume determination, a phantom was used which consisted of a pear shaped balloon filled with a known volume of normal saline with a specific activity of 0·15 MBq/ml and suspended at a depth of 10 cm within a tank of elliptical cross section. The tank was filled

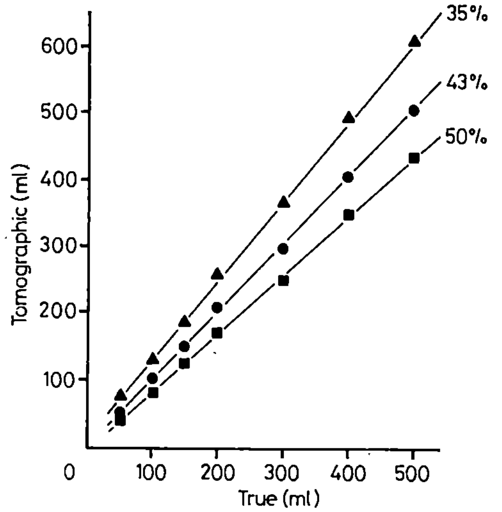

Fig. 3 *Phantom volumes calculated tomographically correlated with true volume. Contours at 35%, 43%, and 50% of maximum counts are used, but 43% contours give volumes closest to the line of identity. The linear regression equations are: 50% contour, $y=1{\cdot}9x+12$, $r=1{\cdot}000$: 43% contour, $y=1{\cdot}01x+0$, $r=1{\cdot}000$: 35% contour, $y=0{\cdot}88x-9$, $r=0{\cdot}999$.*

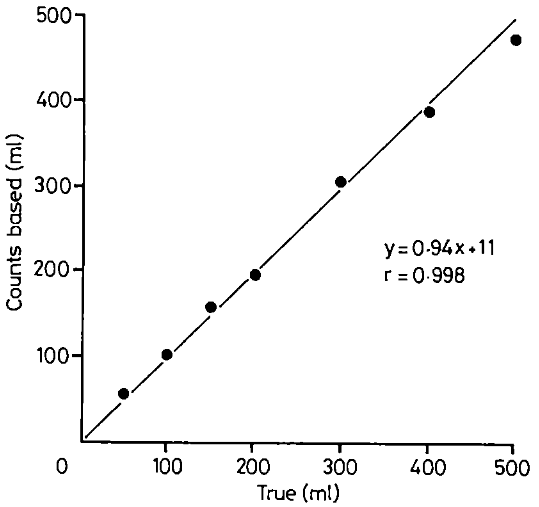

Fig. 4 *Phantom volumes calculated by a counts based method from a planar image.*

with saline of specific activity 0·015 MBq/ml, and the design was intended to mimic a labelled left ventricular cavity within the thorax surrounded by background activity. The volume of the phantom was determined either by summing the areas of the tomographic sections or from the number of counts within a single planar image after correction for background activity and for attenuation.

STUDY POPULATION

A total of 25 patients was studied, of whom six had no demonstrable cardiac abnormality, 16 coronary artery disease (10 with previous infarction), one valvar heart disease, and two congestive cardiomyopathy.

Results

PHANTOM EXPERIMENTS

Figure 3 shows the results of the tomographic method for determining volume, and it can be seen that there is an excellent linear correlation over a wide range of volumes. The value obtained is highly dependant upon the contour used to define the edge of each section, but a contour at 43% of maximum counts within the phantom gives a regression line closest to the line of identity. For this reason a 43% contour was used in the subsequent determination of left ventricular volume. For the sake of brevity the detailed results are not shown here, but the effect of different filters in the reconstruction of the transaxial sections was studied, and as expected filters with heavier smoothing gave higher volumes and vice versa. For instance, filtering with a cutoff frequency of 0·25 increased calculated volumes by 3% and with a cutoff frequency of 0·75 decreased volumes by 3%.

Figure 4 shows the results of the planar counts based method, and again there is an excellent linear correlation.

LEFT VENTRICULAR VOLUMES

Figure 5 shows typical mid-cavity blood pool sections in one of the normal subjects to illustrate the quality of the images that was consistently obtained.

Figure 6 correlates the tomographic and the counts based methods for the determination of left ventricular volume, and both end diastolic and end systolic volumes are included. The individual regression equations for each set of points are shown, and since the difference between these is not statistically significant ($t=0{\cdot}14$, $p>0{\cdot}1$) a single regression line has been drawn through all the points. Standard errors of the slope and intercept are 0·0032 and 6·7 respectively, giving 95% confidence limits of 0·76 to 0·96 for the slope and of 12 to 34 for the intercept. The line of identity lies only just outside these limits. From visual inspection of the data, it appears that the slope is less than 1 either because low volumes are overestimated slightly by the tomographic method or because they are underestimated by the counts based method. This is discussed below.

Given both end diastolic and end systolic volumes, it is possible to calculate ejection fraction, and Figure 7 correlates tomographic ejection fraction with that from the planar study. Again a good correlation is obtained, with a regression line not significantly dif-

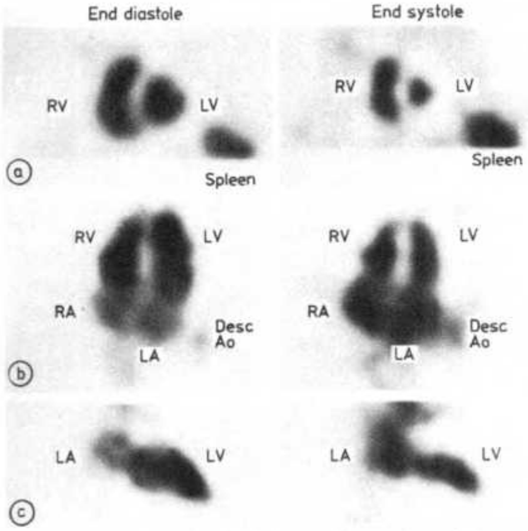

Fig. 5 *(a) Short axis, (b) horizontal long axis, and (c) vertical long axis electrocardiogram gated blood pool sections in a normal subject. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; Desc Ao, descending aorta.*

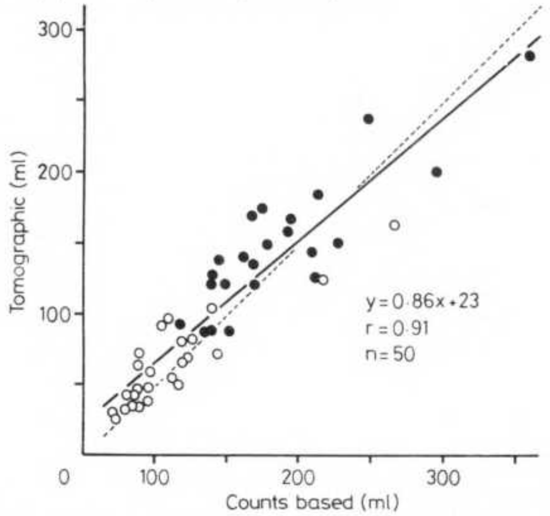

Fig. 6 *Left ventricular volumes calculated tomographically correlated with counts based volumes from a planar radionuclide ventriculogram.* (●) *end diastolic volumes,* (○) *end systolic volumes. The dashed line is the line of identity and the solid line the linear regression line through all the points. The individual regression lines are: end diastole, $y=0{\cdot}71x+55$ ($r=0{\cdot}85$), end systole, $y=0{\cdot}71x+22$ ($r=0{\cdot}88$).*

ferent from the line of identity.

Discussion

INVASIVE TECHNIQUES

The importance and difficulty of determining left ventricular volume can be judged by the length of its history, which goes back at least 70 years.[4] Methods based on x ray contrast ventriculography have been extensively studied and rely on measurements made from either a biplane or a single plane ventriculogram and assume that the left ventricle is the shape of an ellipsoid or of a prolate spheroid respectively. The method first proposed by Chapman *et al*[5] is very similar to that used in this study in that the areas of sections through the left ventricle are summed. This method, however, was too tedious for routine use and was eclipsed by the methods of Arvidsson[6] and Dodge *et al*[7] in which the minor axes of the ellipsoid are either measured directly or calculated from the projected area of the left ventricle. Adaptation of the technique for single plane ventriculograms[8 9] and for oblique biplane ventriculograms[10] has been successful, and the subject has been well reviewed.[11 12]

The major problem of all these methods, however, is that it is necessary to assume a shape for the left ventricle, and this assumption is always incorrect to a greater or lesser extent. Volumes calculated by these methods must therefore be suspect, especially for ventricles of irregular shape. In addition, the effect of rapid injection of contrast medium into the left ventricle is unknown, and there is dispute whether it affects volume[12] or not.[13] Reason predicts that there will be a change in volume over the few contractions after injection, which will depend on the volume and rate of injection and maybe on the timing of injection with respect to the cardiac cycle.

RADIONUCLIDE TECHNIQUES

The above techniques can be applied to a radionuclide

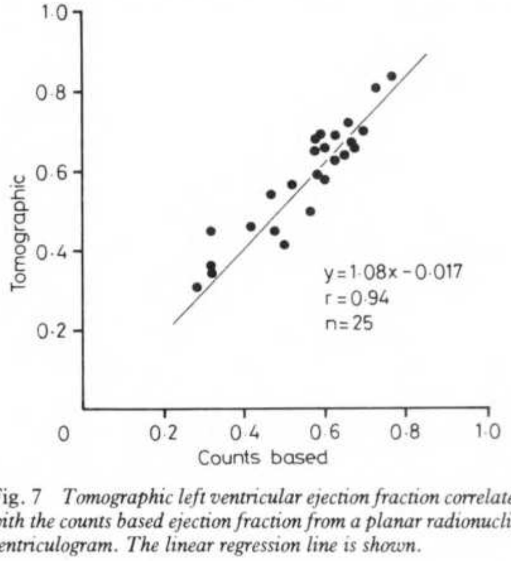

Fig. 7 *Tomographic left ventricular ejection fraction correlated with the counts based ejection fraction from a planar radionuclide ventriculogram. The linear regression line is shown.*

ventriculogram,[14 15] but the relatively poor spatial resolution dictates that non-geometric methods will be better for planar radionuclide studies.[16] Left ventricular volume can be calculated non-geometrically either from a first pass radionuclide ventriculogram,[17–19] or from an equilibrium radionuclide ventriculogram.[20 21] The equilibrium techniques equate counts within the left ventricular image to volume and so make no assumption about shape, but they do suffer from the problem of attenuation of counts by surrounding structures.[22 23] This problem can be overcome in different ways,[2 24 25] and we use a modification of the technique of Links *et al*,[2] in which attenuation is estimated in each patient by measuring the depth of the left ventricle and an attenuation coefficient is assumed. This method has been shown to correlate closely with volumes determined by single plane *x* ray contrast ventriculography. In contrast to Links *et al*, however, we used an attenuation coefficient of $0{\cdot}10\ \mathrm{cm}^{-1}$, which is closer to reality than the theoretical value for water of $0{\cdot}15\ \mathrm{cm}^{-1}$,[3] which pertains to attenuation of a narrow beam of photons by an infinitely thin section of water. Unfortunately, attenuation varies between individuals, and this is the most important source of error in this technique.

ECHOCARDIOGRAPHIC TECHNIQUES

Planar radionuclide methods for the determination of left ventricular volume overcome the geometric problems of contrast ventriculography by equating counts to volume, but it is also possible to overcome them by making multiple measurements in three dimensions. The tomographic method used in this paper is such a method, and its advantage is that it makes no assumptions about the shape of the left ventricle, except that it can be represented by the sum of a series of tomographic sections. Cross sectional echocardiography can also image multiple sections through the heart and has been used to measure left ventricular volume.[26 27] Unfortunately, this is of limited applicability at present for several reasons. Firstly, a complex mechanical arm is required for the ultrasound transducer in order to record the position of each section as it is imaged. Secondly, the short axis sections generated are not parallel but pivot around the transducer head, and, thirdly, it is not always possible to image the whole endocardial surface, especially at the apex. Simpler echocardiographic methods are available,[28] but they all make some assumption about ventricular geometry.

GATED BLOOD POOL EMISSION TOMOGRAPHY

Single photon emission computed tomography is not a new technique,[29] and it has been used before to determine organ volume.[30] It is only recently, however, that commercially available computers have been able to handle electrocardiogram gated emission tomography, and so allow tomographic imaging of the intracardiac blood pools,[31–33] and application of the technique to the determination of left ventricular volume has been limited.[33 34] There are of course problems to be overcome, but the three dimensional representation of the left ventricle obtained suggests that it should become the most direct and accurate method for measuring left ventricular volume.

We have used the horizontal long axis sections to determine volume since in these sections the left ventricular contours are easiest to define. The basal short axis sections can be difficult because of the proximity of the left atrium and aorta, and the septal vertical long axis sections can be difficult because of the proximity of the right ventricle. Even in the horizontal long axis sections it can sometimes be difficult to define the base of the left ventricle, although the position of the mitral and aortic valves can be decided by reviewing all the available sections. It was possible in all our patients to calculate left ventricular volume, whereas Nixon *et al* found only nine of 16 subjects suitable for echocardiographic volume measurements.[27]

A second problem is the choice of contour to use for definition of the endocardium. The phantom experiments show that for the system of acquisition and processing used here 43% of maximum counts within the phantom gives best results. This value will, however, change for different processing methods, and in particular we have shown how back projection, using a filter that produces heavier smoothing, leads to apparently greater volumes. Tauxe *et al* found a 45% contour to give the best results for volumes less than 1 litre,[30] but it is not surprising that the best contour will vary with the processing system used. It will also vary with volume, and below approximately 100 ml a higher percentage contour may be needed since the relatively poor spatial resolution of emission tomography "smears out" the images and in particular makes small objects appear larger.[35] This most likely explains why the tomographic volumes at end systole are slightly larger than the counts based volumes, whereas there is much better agreement at end diastole.

It has also been assumed that the best contour to use is independent of scattering, and, although Tauxe *et al* found different scattering media around a phantom to make little difference to calculated volume,[30] our experience is different. Our phantom was surrounded by water which will have different scattering properties from the soft tissue, lung, and bone surrounding the left ventricle, and this may have some effect. In addition, the best contour to use may vary with the shape of the object studied.[30]

Finally, it is relevant to consider whether 100 ms frames are sufficiently short to determine the volume of a moving object accurately. Hamilton *et al* have shown that in planar radionuclide ventriculography, at 100 ms per frame, end diastolic volume is underestimated and end systolic volume is overestimated by approximately 6%.[36] This, however, is for a counts based method, and for a geometric tomographic method the errors will not be so great, particularly at end diastole. This problem could be overcome by reducing frame duration, but this would mean longer acquisition times for an equivalent number of counts.

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Case reports

Reactive pulmonary hypertension after a switch operation

Successful treatment with glyceryl trinitrate

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SUMMARY After an arterial switch operation (anatomical correction for transposition of the great arteries) in a 6 month old child reactive pulmonary hypertension developed six hours after cardiopulmonary bypass. Intravenous glyceryl trinitrate was the only means by which the pulmonary hypertension could be reversed.

In patients with pulmonary hypertension due to pulmonary vascular disease postoperative mortality is appreciably increased. Episodes of acute reactive pulmonary hypertension have been reported after surgical correction of several congenital cardiac abnormalities.[1 2] To prevent a fatal outcome of these episodes prompt treatment with vasodilating drugs and hyperventilation with pure oxygen is mandatory.[3] Numerous pulmonary vasodilators have been described, but the pulmonary response to all these drugs is unpredictable. Laboratory studies have shown glyceryl trinitrate to be an effective pulmonary vasodilator.[4] It also lowers patients' pulmonary artery pressures considerably.[5 6] To our knowledge glyceryl trinitrate has not previously been used to treat a pulmonary hypertensive crisis in a child after cardiac surgery. We report the successful use of the drug in a case of reactive pulmonary hypertension after a switch operation for transposition of the great arteries.

Case report

Transposition of the great arteries with a large ventricular septal defect was diagnosed in a child on the day of birth. At 6 months (weight 5700 g, length 66 cm) we decided to perform an arterial switch operation and close the ventricular septal defect. At catheterisation one week before operation the following pressures were found: right atrium mean 4, left atrium mean 5, right ventricle mean 77, aorta 72/45 (mean 57), and left ventricle mean 72 mm Hg. The pulmonary artery pressure could not be ascertained during the investigation. The ventricular septal defect was closed with a double velours Dacron patch through the tricuspid valve; the aorta and pulmonary artery were transposed with reimplantation of the coronary arteries into the "new" aorta.[7] Total cardiopulmonary bypass time was 131 minutes, and the aorta was crossclamped for a single period of 78 minutes. After the release of the aortic clamp the heart started beating spontaneously in sinus rhythm at a temperature of 24°C.

Pressures directly after cardiopulmonary bypass were: right atrium mean 3, right ventricle mean 80, pulmonary artery 60/10 (mean 29), left atrium mean 8, left ventricle mean 90, left ventricular end diastolic 14, and radial artery 90/35 (mean 53) mm Hg. The heart rate at this stage was 150 beats/min. The systemic arterial blood gases were: pH 7·49, $Paco_2$ 3·2 kPa (24 mm Hg), Pao_2 53 kPa (400 mm Hg), base excess −3 mmol/l. One hour after cardiopulmonary bypass a 5 French gauge thermodilution Swan-Ganz catheter was introduced percutaneously via the internal jugular vein. The pressures were: right atrium mean 6, right ventricle 60, pulmonary artery 26/15 (mean 21), pulmonary artery wedge and left atrium mean 9, radial artery pressure 90/33 (mean 54) mm Hg.

About 20 minutes later the chest had to be

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reopened because of signs of cardiac tamponade. Inappropriate clotting with diffuse bleeding was found. In the four hours before the chest could be safely closed again fresh frozen plasma, platelets, and one litre of fresh blood were transfused. During the whole of this period the pulmonary arterial systolic pressure was 40–75% of the systemic arterial systolic pressure.

Six hours after the bypass procedure a steady but severe increase in the pulmonary arterial pressures was noted over a period of 20 minutes. The pulmonary artery pressure rose to 123/75 (mean 96) mm Hg, and the systemic pressure at this stage was 112/60 (83) mm Hg. The heart rate (163 beats/min) and cardiac index (5·0 l/min/m^2) remained essentially unchanged. Systemic arterial blood gases were normal: pH 7·44, $Paco_2$ 5 kPa (40 mm Hg), Pao_2 35 kPa (259 mm Hg), base excess +4 mmol/l. The oxygen saturations were 68, 72, and 96% in the superior vena cava, pulmonary artery, and radial artery respectively. Serum glucose and calcium concentrations were normal. Hyperventilation with pure oxygen, injection of 7 μg/kg fentanyl and 0·7 μg/kg isoprenaline intravenously, and injection of 1 μg/kg prostaglandin E_1 directly into the pulmonary artery all had no effect on pulmonary hypertension. A bolus injection of 10 μg glyceryl trinitrate intravenously lowered the pulmonary artery pressure to 74/49 (57) mm Hg without lowering the systemic pressure. This favourable change was maintained by a continuous infusion of glyceryl trinitrate 12 μg/kg/min. Thirty six hours later it was decreased and stopped 72 hours postoperatively. During this period the pulmonary arterial systolic pressure never rose above 70% of the systemic arterial systolic pressure and gradually decreased to 40%. The cardiac index remained between 3·7 and 4·6 l/min per m^2. On the fourth postoperative day he was extubated and 10 days later discharged home without any further postoperative complications.

Discussion

Pulmonary hypertension often occurs in patients with cardiac disease associated with an appreciable increase in pulmonary blood flow.[8] The increased flow stimulates the growth of muscle fibres in the pulmonary artery. Before irreversible pulmonary hypertension develops three histological components are present: increased muscularity of the small pulmonary arteries, hyperplasia of the intima, and a decrease in the number of intra-acinar arteries.[9]

Histological studies have indicated that the reactivity of the pulmonary vascular bed to vasoconstrictor agents is noticeably increased in these preconditioned arteries.[2 9–11] Hypoxia, acidosis, hypercapnia, microatelectasis,[1 2 12] hyperinflation,[13] cold environment,[14] aspiration,[3] and, especially in neonates, hypocalcaemia, hypoglycaemia, or polycythaemia[2] may all act as stimuli for reactive pulmonary vasoconstriction to develop postoperatively. Pulmonary hypertension may accompany episodes of systemic hypertension during light general anaesthesia.[15] Acute pulmonary hypertension may occur during withdrawal from cardiopulmonary bypass or after withdrawal of ventilatory support but also without any obvious cause during apparently optimal ventilation.[1 2 16]

None of the above known stimuli was present in our patient. Detachment of the ventricular septal defect patch was a consideration but could be ruled out as there was no appreciable increase in the oxygen saturation between the right atrium and the pulmonary artery. Administration of one litre of blood could have led to the development of pulmonary hypertension by infusion of microaggregates, but the blood was less than 12 hours old and therefore unlikely to have formed microaggregates.[17] Extensive laboratory investigations also failed to show any sign of intravascular clotting.

Hyperventilation with pure oxygen, fentanyl, and isoprenaline failed to change the pulmonary artery pressure. Prostaglandin E_1 dilates the pulmonary as well as the systemic vessels. The effect on the pulmonary circulation is unpredictable,[18 19] and our patient did not respond to a relatively high dosage of 1 μg/kg infused directly into the pulmonary artery. Tolazoline has successfully been used in the treatment of pulmonary vasoconstriction,[1 2 20] but because we had previously noted an equal fall in the systemic and pulmonary arterial pressures tolazoline was not used.

Sodium nitroprusside and glyceryl trinitrate relax the musculature of both the systemic and pulmonary vessels. At normal dosages glyceryl trinitrate mainly effects the venous system without lowering the systemic arterial pressure unduly.[5 6] The action of sodium nitroprusside on the pulmonary vessels normally becomes effective only after considerable changes in systemic resistance and pressure[21 22]; its successful use has, however, been reported in a patient who could not be weaned off cardiopulmonary bypass because of pulmonary hypertension.[16]

Methaemoglobinaemia can be a complication of treatment with intravenous glyceryl trinitrate. At infusion rates of less than 7 μg/kg/min the methaemoglobin concentration, normally less than 1 g/dl, does not exceed 2 g/dl.[23] The maximum dosage used in our patient was 12 μg/kg/min, at which rates it may be advisable to monitor methaemoglobin concentrations. The extent to which the ratio between the pulmonary and systemic arterial pressures should be lowered postoperatively is not known. In a retrospective study of ventricular septal defects it appeared that a preoperative ratio of <0.45 was associated with the lowest postoperative mortality.[24] Increases in the pulmonary arterial pressure $>60\%$ of the systemic arterial pressure have been reported to be dangerous and should be lowered if possible.[25]

Treatment of reactive pulmonary hypertension must be prompt to prevent acute dilatation and failure of the right ventricle.[1] Glyceryl trinitrate has been found to be an effective pulmonary vasodilator, and we think that its use should probably be recommended in preference to other more generally used drugs because a minimal and predictable effect on the systemic pressure is achieved while cardiac output is increased.

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Unruptured right coronary sinus to left ventricle aneurysm diagnosed by cross sectional echocardiography

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SUMMARY A 37 year old Chinese man presenting with features of chest infection was diagnosed as having severe aortic regurgitation. Cross sectional echocardiography showed an intact right coronary sinus of Valsalva aneurysm, which protruded into the left ventricle. The changes in appearance of the aneurysm during the cardiac cycle were recorded by cross sectional echocardiography. The opening of the aneurysm was successfully closed and the aortic valve replaced with a mechanical prosthesis.

Although uncommon, a sinus of Valsalva aneurysm is a well known clinical entity. Most aneurysms of the sinus of Valsalva originate in the right coronary sinus and penetrate into either the right ventricle or atrium.[1 2] An aneurysm of the right coronary sinus which extends into the interventricular septum and protrudes into the left instead of the right ventricle is exceedingly rare. To our knowledge, only a few cases have been reported.[3] Of the patients reported, all had ruptured aneurysms except one.[3] Recently, we encountered a patient with severe aortic regurgitation secondary to an unruptured right coronary sinus aneurysm, which extended into the left ventricular outflow tract and protruded against the ostium of the left ventricle. The aortic sinus aneurysm was diagnosed by cross sectional echocardiography and subsequently confirmed by angiography and at operation. Because of the rarity of the anatomical anomaly and because the cross sectional echocardiographic features of such an aneurysm have not been described before, we report this case.

Case report

A 37 year old Chinese man was admitted to hospital in December 1983 with progressive exercise intolerance during the past two months and a cough of two weeks' duration. The cough produced yellowish sputum, which was occasionally blood streaked. He was afebrile, and there was no history of notable past illnesses. At physical examination on admission his general condition was satisfactory. There was no evidence of congestive heart failure. His blood pressure was 140/50 mm Hg and his pulse 90 beats/min, regular, and collapsing in character. The heart was enlarged with a left ventricular impulse, and the apex beat was in the sixth intercostal space 2 cm lateral to the midclavicular line. A 3/6 ejection systolic and an early diastolic murmur were heard along the left sternal border. Coarse inspiratory and expiratory crackles were present over the right lung base. Laboratory data showed no abnormalities. The electrocardiogram showed sinus tachycardia and features of left ventricular hypertrophy. A chest radiograph showed cardiomegaly (cardiothoracic ratio 0·61) and diffuse mottling over the right lung.

Echocardiography indicated a grossly dilated left ventricle (left ventricular end diastolic dimension 7·5 cm and end systolic dimension 5·5 cm). The aortic root was 3 cm in diameter, and the aortic valve had three cusps. A 2 cm lobulated pulsating mass dominated the subaortic area and was readily seen in the parasternal long axis and short axis views as well as in the apical four chamber view (Fig. 1). The mass extended from the region of the right coronary cusp to the adjoining interventricular septum. In the parasternal long axis view it enlarged during diastole and descended into the left ventricle during diastole and moved towards the anterior leaflet of the opened

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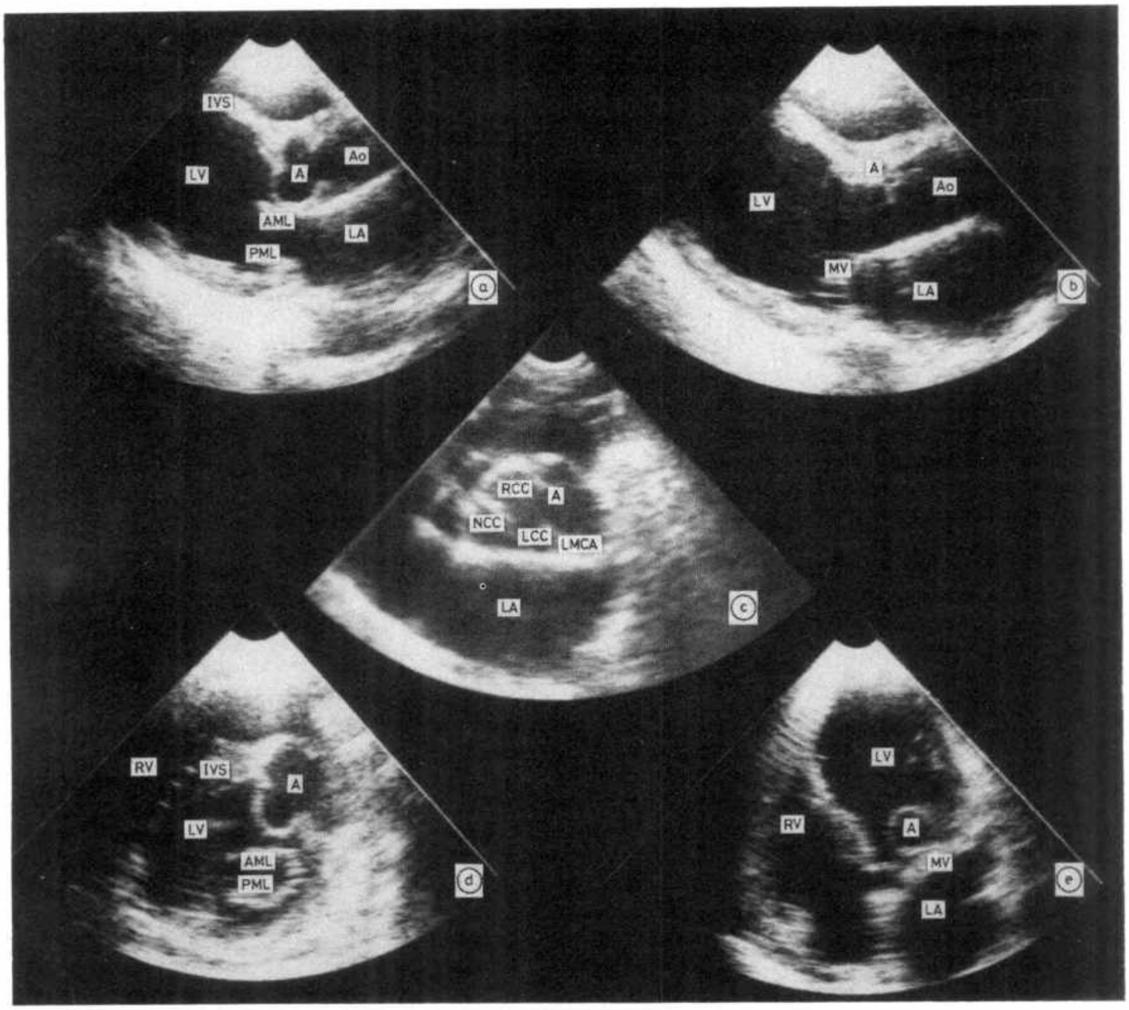

Fig. 1 *Cross sectional echocardiograms of the unruptured right coronary sinus of Valsalva aneurysm in (a) the parasternal long axis view at end diastole; (b) the parasternal long axis view at end systole; (c) and (d) the parasternal short axis views and (e) the apical four chamber view. A, aneurysm; Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle; IVS, interventricular septum; MV, mitral valve; AML, PML, anterior and posterior mitral leaflets respectively; LMCA, left main coronary artery.*

mitral valve. At end diastole it almost filled the left ventricular outflow tract (Fig. 1a). In systole it contracted down and almost disappeared at end systole (Fig. 1b). The mitral valve moved normally, and diastolic fluttering of the anterior leaflet was evident. The cross sectional echocardiographic features were compatible with severe aortic regurgitation, and we thought that the pulsating mass could be an unruptured aneurysm of the right coronary sinus of Valsalva.

In view of the clinical and radiographic features of concomitant chest infection, the patient was treated with erythromycin after sputum samples were taken for bacterial, including mycobacteria, and viral culture. Nevertheless, all cultures yielded no growth, and there was no improvement in his chest radiograph after four weeks. Bronchoscopy with a fibreoptic bronchoscope did not show any endobronchial lesion. Cultures of bronchial aspirates were also negative. A transbronchial biopsy specimen showed features of organising pneumonia. He was then given a course of intravenous tobramycin and cefotaxime empirically. The radiographic mottling in the right lung field gradually resolved over the following three weeks.

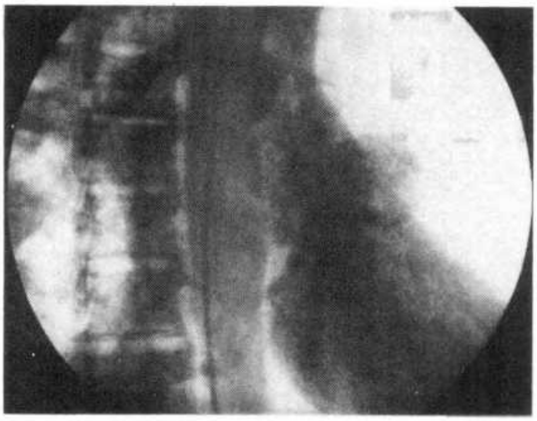

Fig. 2 *Angiogram of aortic root in the right anterior oblique view. There is filling of the aneurysm and aortic regurgitation.*

While awaiting further investigation and cardiac surgery he developed acute left heart failure and pulmonary oedema. This was successfully controlled with a diuretic and a vasodilator. Repeated echocardiographic examination showed similar features with further left ventricular dilatation and development of premature closure of the mitral valve. Immediate cardiac catheterisation showed a mean pulmonary artery pressure of 40 mm Hg, a mean pulmonary artery wedge pressure of 34 mm Hg, and a left ventricular end diastolic pressure of 24 mm Hg. The cardiac index was 1·44 l/min per m^2. No pressure gradient nor intracardiac shunt were found. A cineangiogram (Fig. 2) confirmed severe aortic regurgitation and the presence of an unruptured aortic sinus aneurysm.

OPERATIVE FINDINGS AND REPAIR

Surgery was performed with the aid of cardiopulmonary bypass and cold chemical cardioplegia. Except for the severe left ventricular hypertrophy, the heart and great vessels were normal externally. At aortotomy the aortic valve consisted of three cusps, the left and non-coronary cusps being slightly thickened and near normal size. The right coronary cusp was small, fibrotic, and centrally displaced. This small deformed cusp was probably the cause of the aortic regurgitation. A 15 × 10 mm opening was present in the left and central parts of the right coronary sinus of Valsalva. It was bounded posteromedially by the displaced right coronary cusp and anterolaterally by the aortic wall. It appeared as if the aortic valve annulus at the right coronary sinus had been detached from the aortic wall. This opening led to a lobulated, smooth surface cul de sac in the interventricular septum. When this sac was filled with fluid it bulged into the left ventricle towards the anterior leaflet of the mitral valve. The coronary ostia were normal, and there was no other abnormality at the aortic root. An attempt was made to reattach the displaced right coronary cusp to the aortic wall. Nevertheless, this further distorted the aortic valve, which was then excised. The remnant of the right coronary cusp was sutured to the aortic wall by several horizontal mattress sutures buttressed with teflon felt pledgets. This removed the aneurysm completely from the aortic root. A 25A Medtronic Hall valve was then sutured in the subcoronary position. The heart was defibrillated without difficulty and resumed normal function. The right pleural cavity was explored through the sternotomy incision, and one litre of straw coloured fluid was sucked out. The right lung appeared to be oedematous but otherwise normal. The patient was returned to the intensive care ward in a satisfactory condition.

Thirty six hours after the operation, he developed recurrent ventricular tachycardia and episodes of transient complete heart block. Each episode of arrhythmia was accompanied by low cardiac output. The arrhythmia was finally controlled with intravenous amiodarone and temporary atrial pacing. Acute renal failure developed, which was treated with haemodialysis. He gradually recovered and was discharged from hospital one and half months after the operation. At follow up one month later he was asymptomatic, and repeated echocardiographic examination showed only a dilated left ventricle with a normal functioning aortic prosthetic valve.

HISTOPATHOLOGY

Histopathological examination of the excised aortic valve cusps showed patchy hyalinisation and areas of myxomatous change particularly of the fibrosa. The appearance suggested a degenerative lesion. Biopsy of the aortic wall showed hyalinised thickening of the intima, and the media appeared to be deficient in one part of the section. Right lung biopsy showed moderate congestion, patchy fibrosis particularly of interlobular regions, and patchy thickening of interalveolar septa with mild sclerosis of small vessels. Subpleural fibrosis with infiltration by lymphocytes, plasma cells, and some macrophages was also present. The features were those of moderate passive congestion with patchy fibrosis.

Discussion

Aneurysm of sinus of Valsalva is a morphological diagnosis and includes both congenital and acquired aneurysms. Acquired aneurysms are mainly due to syphilis, tuberculosis, or infective endocarditis. As pointed out by Sakakibara and Konno,[2] the site of origin and direction of dilatation of congenital aortic sinus aneurysms follow a definite pattern. They are determined by the developmental process in the embryonic period. Over 95% of aneurysms originate in the right coronary sinus and right part of the noncoronary sinus and protrude into the right ventricle or atrium. On the other hand, acquired aneurysms affect tissues at random and protrude or rupture in directions that are inexplicable by embryology. In our patient, there was no clinical or pathological evidence of syphilis, tuberculosis, or infective endocarditis. His right coronary sinus aneurysm probably belonged to the classification of pseudoaneurysms as described by Sakakibara and Konno.[2] These aneurysms develop after intramural rupture of a congenital aneurysm with subsequent formation of a haematoma and organisation. What initiated the intramural rupture in our patient is unexplained.

The extension of an unruptured aortic sinus aneurysm into the interventricular septum and thence into the left ventricle is extremely rare. Only one case has been reported by Metras and associates.[3] In their report they cited seven other cases seen by French workers, which are not available to us. They stated that the French workers reported that septal extension of an aortic sinus aneurysm might present as mitral regurgitation because of displacement of the anterior mitral leaflet. In our patient, however, the cross sectional echocardiograms clearly showed that the unruptured right coronary sinus to left ventricle aneurysm would not interfere with the mitral valve mechanism. A very large aneurysm, especially in the presence of atrial fibrillation, might interfere with the opening of the anterior mitral leaflet. Severe aortic regurgitation will certainly cause premature mitral valve closure. Nevertheless, an unruptured aneurysm per se is unlikely to cause mitral regurgitation.

With the advent and wide application of echocardiography, an unruptured aortic sinus aneurysm will be diagnosed at the bedside and no longer be "one of the silent congenital lesions to be suspected when bacterial endocarditis develops in a heart apparently previously healthy."[1]

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Myocardial infarction with normal coronary arteries and factor XII deficiency

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SUMMARY A 17 year old girl had a myocardial infarction. Three days later coronary angiography showed an occlusive thrombus in the circumflex and anterior descending arteries. The coronary arteries themselves appeared to be normal, and this was confirmed at repeat angiography three months later. Tests of haemostasis showed a deficiency of factor XII.

Most patients with acute myocardial infarction have atherosclerotic coronary disease, but subsequent coronary angiography sometimes does not show any evidence of chronic arterial obstruction.[1 2] Spontaneous lysis of a thrombotic occlusion and resolution of spasm are two possible explanations for such observations, and both have been known to cause myocardial infarction as a complication of coronary angiography.

We recently showed an occlusive thrombus by coronary arteriography in a 17 year old girl three days after acute myocardial infarction; repeat angiography three months later showed normal coronary arteries. Tests of haemostasis confirmed a factor XII deficiency, a condition that has previously been associated with the occurrence of spontaneous intravascular thrombosis.[3]

Case report

A 17 year old girl was admitted to hospital having vomited and collapsed at home. On admission she was fully conscious but complained for the first time of severe pain in the centre of her chest that radiated through to her back. She had previously been well with no relevant history, and there was no family history of heart disease. She had smoked about 10 cigarettes daily for two years but was not taking the contraceptive pill.

Physical examination yielded normal results apart from a pulse rate of 120 beats/minute, and her blood pressure was 110/80 mm Hg. Serial electrocardiograms showed evolving changes in the ST segment, T wave, and Q wave typical of acute transmural inferolateral myocardial infarction. Serum aspartate transaminase activity rose to 166 IU/l (normal range 0–18 IU/l) and hydroxybutyrate dehydrogenase activity to 1108 IU/l (normal range 0–140 IU/l). Twenty four hours after admission she developed an apical third sound and crepitations at both lung bases, and her chest radiograph showed pulmonary oedema. These signs resolved after treatment with oral frusemide. Three days after admission she underwent coronary angiography and left ventriculography. These showed extensive lobulated filling defects in the left anterior descending and circumflex coronary arteries (Fig. 1). The left main and right coronary arteries were normal. The left ventriculogram showed extensive apical akinesia with mural thrombus. Treatment with warfarin was started. Her subsequent progress was uncomplicated, and the diuretic was stopped when she was discharged from hospital 10 days after admission.

The possibility that a venous thrombus may have embolised to the coronary circulation was explored by cross sectional echocardiography with contrast; there was no evidence of right to left shunting during a Valsalva manoeuvre. Three months later coronary arteriography was repeated. The coronary arteries appeared to be entirely normal (Fig. 2), and the clot previously seen in the apex of the left ventricle had disappeared. The anteroapical segment, however, remained akinetic. Treatment with warfarin was stopped, and she was subsequently given aspirin 300 mg daily and dipyridamole 100 mg thrice daily. A full blood count, measurement of erythrocyte sedimentation rate and electrolyte concentrations, and liver function tests yielded normal results. Tests for antinuclear factor were negative, and fasting lipid and cholesterol concentrations were normal.

Requests for reprints to Dr W J Penny, London Chest Hospital, Bonner Road, London E2 9JX.

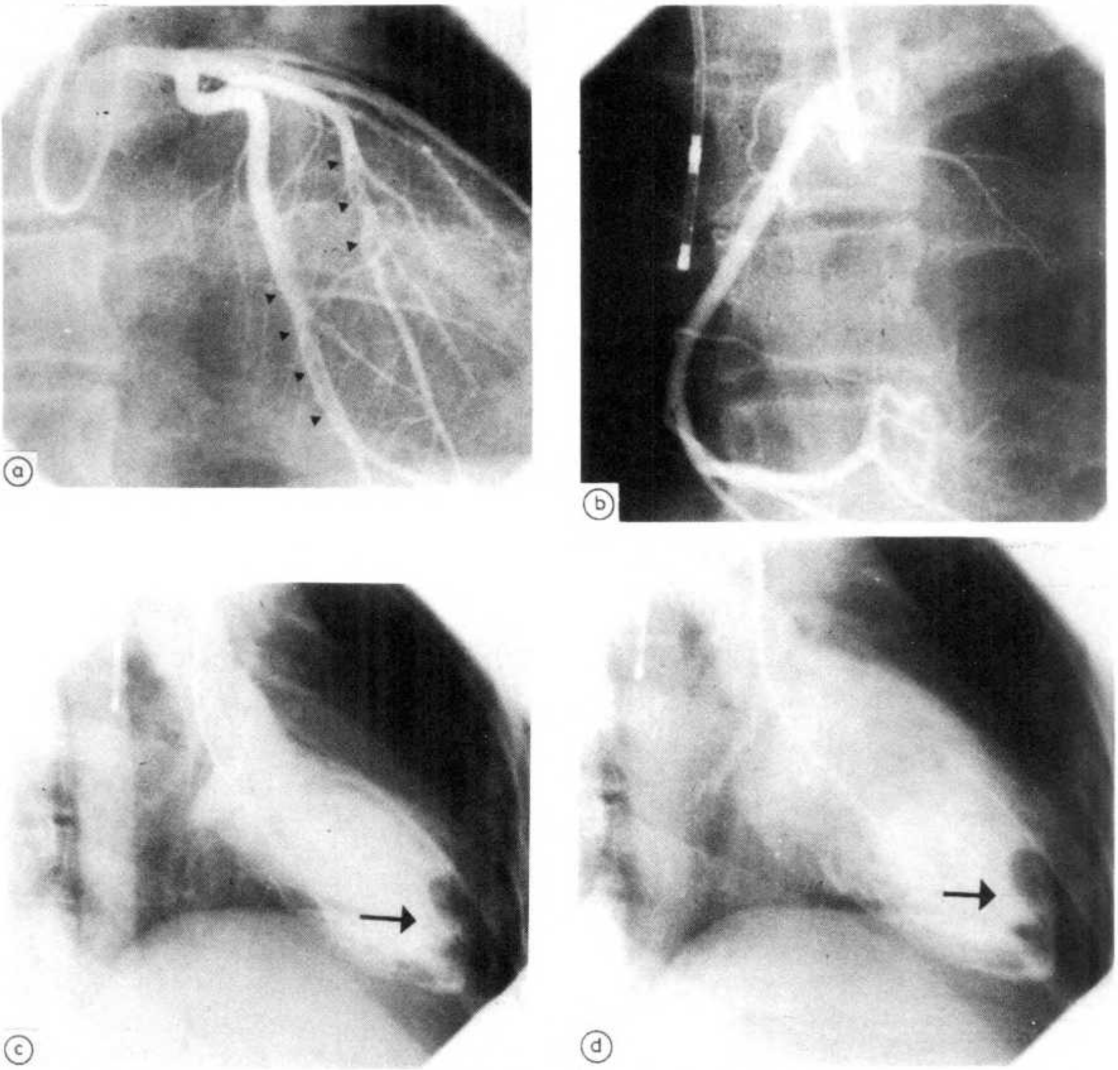

Fig. 1 *Coronary arteriogram three days after onset of symptoms. (a) There were lobulated filling defects (arrowheads) in the left anterior descending and circumflex arteries. (b) The right coronary artery was normal. (c) and (d) The left ventriculogram in the right anterior oblique projection in systole (c) and diastole (d) showed extensive apical akinesia with mural thrombus (arrow).*

TESTS OF HAEMOSTASIS

Blood was taken by clean venepuncture into 3·13 % HEPES buffered sodium citrate at a dilution of one to 10. Plasma rich in platelets was prepared by centrifugation at 250 *g* for 10 minutes and plasma low in platelets by centrifugation at 2000 *g* for 20 minutes. The prothrombin time was measured with British Comparative Thromboplastin and the kaolin cephalin time with a commercial kit (Diagnostic Reagents Limited, Thame). The thrombin time reagent was a mixture of thrombin and calcium chloride adjusted to give a control time of 10 seconds.

Factor VIII concentration was measured by a method in two stages (Diagnostic Reagents Limited, Thame) and concentrations of factors IX, XI, and XII and prekallikrein were measured by one stage assays with known deficient plasmas as substrate.[4] A test system for the assay of high molecular weight kininogen was not available. Antithrombin III and antiplasmin concentrations were assayed by amidoly-

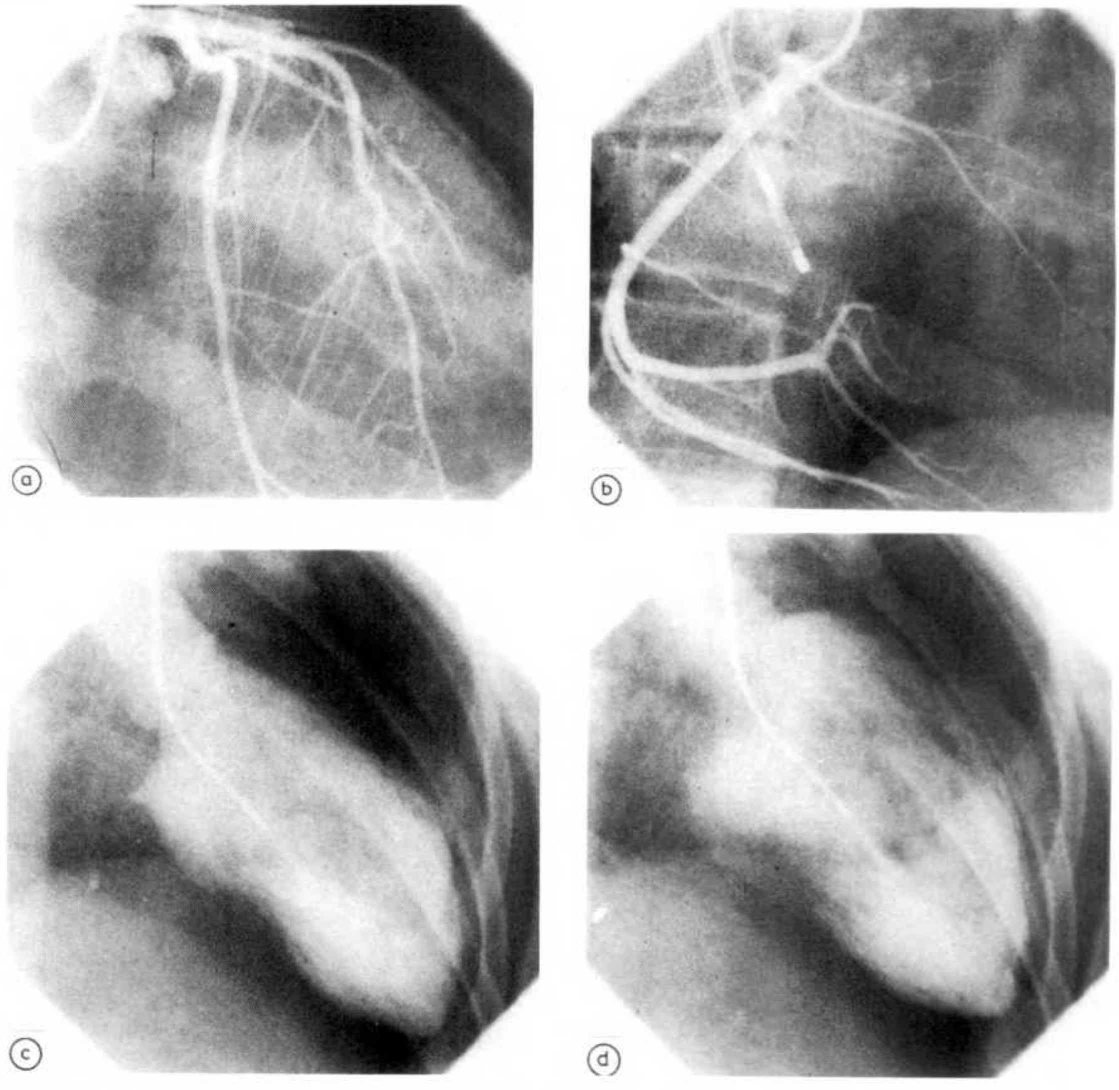

Fig. 2 *Coronary arteriogram three months after myocardial infarction. (a) and (b) Coronary arteries are normal. The left ventriculogram in systole (c) and diastole (d) continued to show extensive apical akinesia but the mural thrombus had resolved.*

tic methods (Kabi Diagnostica, Stockholm), protein C by Laurell electrophoresis, and plasminogen by a caseinolytic method. Fibrinolytic activator was measured by placing euglobulin precipitates on unheated fibrin plates and assessing zones of lysis after incubation overnight. Platelet function tests were done in an axiodistogingival aggregometer with standard concentrations of adenosine diphosphate, adrenaline, collagen and ristocetin.

These investigations (Table) showed a prolonged kaolin cephalin time owing to a partial deficiency of factor XII (Hageman factor), which was 27% of the control concentration. There was no evidence of inhibitory activity, and tests for the lupus inhibitor gave negative results. These findings were confirmed on two subsequent occasions and in an independent laboratory. Platelet aggregation induced by diminished adrenaline and collagen concentrations

Table *Results of tests for haemostasis. These findings were confirmed on two subsequent occasions and in an independent laboratory*

	Patient	*Control*	*Normal range*
Prothrombin ratio	1·3	1	110–1·3
Kaolin cephalin time (s)*	60	42	35–48
Thrombin time (s)	10	10	10–12
Factor VII (IU/ml)	0·9		0·5–2·0
Factor IX (IU/ml)	0·6		0·5–2·0
Factor XI (%)	82		50–200
Factor XII (%)	27		50–200
Prekallikrein (Fletcher) (%)	64		50–200
Antithrombin III (IU/ml)	0·91		0·8–1·2
Protein C (%)	95		Not established
Antiplasmin (%)	130		2–4
Euglobulin lysis zone (mm^2)	87	88	60–100

*Equal volume mix of normal and test plasma 42 s.

was compatible with treatment with aspirin.

Discussion

Our patient showed unequivocal electrocardiographic, cardiac enzyme, and angiographic evidence of acute myocardial infarction. Coronary angiography at three days showed extensive filling defects, which had the appearance of thrombus, in the left coronary circulation. The coronary arteries themselves appeared to be normal, and this was confirmed by repeat angiography three months later.

One previous case report has described this sequence, but the 29 year old man reported on was subsequently found at necropsy, four months after angiography gave "normal" results, to have a 75% atherosclerotic stenosis at the site of the previous occlusion.[5] Angiography is highly unlikely to have failed to detect appreciable atheromatous disease in the young woman we have described.

In some cases a prolonged episode of coronary vasospasm may be responsible for myocardial infarction in the absence of coronary atherosclerosis. A thrombotic occlusion could theoretically result from stasis caused by prolonged coronary spasm, and this was recently reported in a case of myocardial infarction that complicated selective coronary angiography.[6] We have no evidence that spasm played a part in our patient. The hypothesis that spasm of the main left coronary artery caused thrombosis distally in its two branches is, however, attractive. Another remote possibility is that coronary spasm caused extensive infarction and there was subsequent embolisation from the mural thrombus, but this would seem to be a suprising coincidence. We found no evidence of a potential for paradoxical embolism.

The finding of a moderate deficiency of factor XII was unexpected. Factor XII is important not only in the intrinsic coagulation pathway but also in plasminogen dependent fibrinolysis, the kallikrein-kinin system, and complement activation.[7] The absence of a tendency to bleed abnormally in most cases of factor XII deficiency together with the reported incidence of thromboembolism[7,8] suggests that these other reactions may be of clinical importance. Both these reports[7,8] include the evidence of reduced fibrinolytic capacity, but this could not be shown in our patient. At least two cases of myocardial infarction in patients with factor XII deficiency have been reported,[9,10] but both patients were middle aged and probably had coronary artery disease.

In reports of myocardial infarction with subsequently normal coronary arteries the aetiology of the presumed thrombotic occlusion has not been known except when it has complicated coronary angiography and has been caused by a catheter.[6] An analysis of conventional risk factors has implicated smoking induced thrombosis,[11] but this has not been an important risk factor in other series,[12] and, although factor XII deficiency could theoretically be relevant in our patient, the association might be coincidental. Long term follow up over many years may provide further clues, but the present case suggests that we need to extend our concept of classical risk factors in young patients with myocardial infarction and normal coronary arteries.

We thank Dr R Balcon, consultant cardiologist, London Chest Hospital, for permission to report this case; and Dr P B A Kernoff, codirector of the haemostasis unit, Royal Free Hospital, for his help with the assays of prekallikrein, protein C, antiplasmin, and plasminogen.

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Br Heart J 1985; **53**: 235–6

Correspondence

Accuracy of angiographic appearances of the coronary arteries

Sir,

The assertion by J Pidgeon *et al* (1984; **51**: 125–9) that their findings are at variance with our observations on the "underfilled" coronary artery[1] is not entirely correct. In our retrospective series of arteries that had been grafted, some vessels that were smaller than 1·5 mm on the preoperative angiogram were patent at one month and appeared larger on the postoperative angiogram. Some were filled by visible collaterals and some were not. Pidgeon *et al* found that when vessel diameter alone was used as a predictive test 26% of vessels thought too small were, at surgery, graftable; there was no postoperative assessment of these vessels. We consider that these two series are complementary, and the inference to be made is that some of the graftable but angiographically small vessels of Pidgeon *et al* may well have been "underfilled."

Their finding that arteries of reasonable size were only 85% suitable for grafting is probably due to an optimistic choice of critical diameter of 1 mm. Certainly, graft survival at or below 1 mm diameter is very poor.[2 3] It would be interesting to know what their figures would be at 1·5 mm diameter.

J B Partridge,
Prince Charles Hospital, Brisbane, Australia;
P W T Brandt,
Greenlane Hospital, Auckland, New Zealand

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This letter was shown to the authors, who reply as follows:

We are grateful to Partridge and Brandt for their interest in our paper. To the extent that 27% of vessels considered small on angiographic assessment and which filled via collaterals were later found to be suitable to receive grafts we agree that our observations may be complementary. The point we wished to make was that we also made erroneous prediction of calibre for normally filled branches, and our ability to predict lumen diameter did not deteriorate significantly for those filled via collaterals (predictive accuracy 84% *vs* 78% respectively). We submit that when these vessels appear small on the angiogram they are still likely to be too small to graft at operation, although on occasions our predictions were wrong. Some of these vessels may be "underfilled" and appear inappropriately small on the preoperative angiogram owing to reduced perfusion pressure. Many collaterally filled vessels were only faintly opacified so that estimation of size becomes more difficult but is still possible with reasonable accuracy. In this context details of angiographic technique may be relevant.[1]

Our figure for angiographic predictive accuracy in assessing suitability for grafting using a cut off point of 1·0 mm was 76%, while the comparable figure at 1·5 mm was 73% (unpublished data). These data relate to the measurements of lumen diameter on the angiogram, and as discussed in our paper prediction (using a value of 1·0 mm) was better using the consensus assessment of the three angiographic observers (85%). Subsequent graft patency is an important issue but not one directly addressed in our study. It seems probable, and the data of Lésperance *et al* support this, that the chance of graft survival is not distributed in a dichotomous manner pivoted about a critical value for lumen diameter but varies over a range of values in the region of 1·0 to 2·0 mm. The choice of a particular value in our study is to some degree arbitrary. A value of 1·2 mm was used by Gohlke *et al.*[2]

We suggest that an attempt at grafting to a vessel of diameter of 1·0 mm may still be worth while, although we accept that the prospect of lasting patency is relatively diminished. The recent observations of Levin *et al*[3] support this premise.

J W Pidgeon,
Broadgreen Hospital, Liverpool L14 3LB.

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Submaximal exercise testing early after myocardial infarction

Sir,
Exercise testing after myocardial infarction has undoubted prognostic value.[1,2] Controversy remains, however, about both the reproducibility and sensitivity of such tests[3,4] and is compounded by differences in patient selection, timing, and drug treatment.

Sullivan, Davies, and Sowton (1984; 52: 147–53) exercised 74 postinfarction patients and obtained a positive result in 54 (73%). Twelve patients were, however, taking beta blocking drugs, five of these having a negative test and a further two being limited by fatigue alone. Moreover, in four beta blocked patients there was an inadequate blood pressure response to exercise.

Others have drawn attention to the possible reduction in sensitivity of the exercise test in patients receiving beta blockers,[5] and in a subsequent report Sowton and colleagues concede that "beta blockers may blunt haemodynamic responses and mask ischaemic changes."[4]

We have found that beta blockade invariably affects ST segment changes of the predischarge test, the degree of ST segment shift after beta blockade being reduced or indeed absent depending on the initial magnitude of such elevation/depression. End points may also be affected—for example, that of fatigue replacing those of ST changes or angina before beta blockade.

Patients with myocardial infarction receiving short term treatment with beta blockers should therefore have their drugs withheld before the predischarge test if this is to be of optimal sensitivity.

N Wilkes,
J Watkins,
St Mary's General Hospital,
Portsmouth, Hants.

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Notices

British Cardiac Society

The Annual General Meeting for 1985 will take place in Birmingham on 17 and 18 April 1985, and the closing date for receipt of abstracts was 8 January 1985. On the second day of the Meeting (18 April) the Society, in conjunction with the Association of Physicians, will hold a one day symposium in commemoration of the bicentenary of the publication of William Withering's account of the foxglove. Only a limited number of places will be available for non-members, who should direct their inquiries to: Professor W A Littler, Department of Cardiovascular Medicine, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.

Doppler ultrasound in the assessment of cardiovascular function

A one day meeting organised by the International Cardiac Doppler Society is to be held at the Great Western Royal Hotel, London W2, on 1 March 1985. Further information may be obtained from: Dr A M Salmasi, St Mary's Hospital, London W2.

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Editor: **H. D. Bolte**

1984. 119 figures, 45 tables.
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Renowned cardiologic researchers and clinicians from around the world have compiled information on all relevant aspects of viral heart disease. Their contributions reflect the most recent insights drawn from animal experimental and clinical studies and cover the pathogenesis, diagnosis and treatment of viral infections as well as their role in dilated cardiomyopathies.

Coronary Artery Diseases

Diagnostic and Therapeutic Imaging Approaches

By **M. Amiel, A. Maseri, H. Petitier, N. Vasile**

1984. 175 figures, 15 tables. XI, 236 pages
Hard cover DM 128,–
ISBN 3-540-13209-0

This guide to the possible uses of today's imaging techniques provides illustrated coverage of conventional X-ray techniques, nuclear medicine procedures, angiographic exploratory techniques and their normal results, pathological findings and significance in surgical intervention, and the complementary role of other procedures such as echocardiography, CT scans and transluminal coronary angioplasty.

Silent Myocardial Ischemia

Editors: **W. Rutishauser, H. Roskamm**

1984. 71 figures, 49 tables.
XVII, 204 pages
Soft cover DM 68,–. ISBN 3-540-13193-0

The high incidence of asymptomatic coronary artery disease or even myocardial infarction makes an understanding of silent myocardial ischemia increasingly important. This book offers an overview in which reliable methods for the detection of and guidelines for the treatment of asymptomatic myocardial ischemia are explored.

Progress in Ergometry: Quality Control and Test Criteria

5th International Seminar on Ergometry

Editors: **H. Löllgen, H. Mellerowicz**
Technical Assistance: I. Heidelbach

1984. 104 figures, 88 tables.
XII, 275 pages
Soft cover DM 54,–. ISBN 3-540-13570-5

This book contains recommendations made at the 5th International Seminar on Ergometry for quality control in ergometry and test criteria and provides a foundation for control standards and comparison in the field.
The topics center on the method of approach, the calibration of the apparatus, the usefulness of lean body mass and the role of lactate analysis. New aspects of ergometric diagnosis such as stress-ECGs, blood pressure response to exercise and athletic testing, are introduced.

C. L. Lake

Cardiovascular Anesthesia

1985. 165 figures. X, 467 pages
Hard cover DM 165,–. ISBN 3-540-96028-7

This book provides the anesthesia trainee with the essential pathophysiologic, hemodynamic and pharmacologic information necessary for skillful handling of patients during cardiac or noncardiac surgery. All aspects of both adult and pediatric cardiac anesthesia – pre-, intra-, and postoperative – are covered.

F. Z. Meerson

Adaptation, Stress, and Prophylaxis

Translated from the Russian by J. Shapiro

1984. 87 figures, 61 tables. X, 329 pages
Hard cover DM 118,–. ISBN 3-540-12363-6

The mechanism of phenotypic adaptation, a key issue in biology and medicine, is investigated in this book. The concept presented shows that phenotypic adaptation can be applied to prevent disease and increase the organism's resistance.

Prognosis of Coronary Heart Disease Progression of Coronary Arteriosclerosis

International Symposium Held in Bad Krozingen, October 22–23, 1982

Editor: **H. Roskamm**

1983. 94 figures, 80 tables. XI, 248 pages
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J. Møller, H. Einfeldt

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1984. 3 figures, 24 color photographs.
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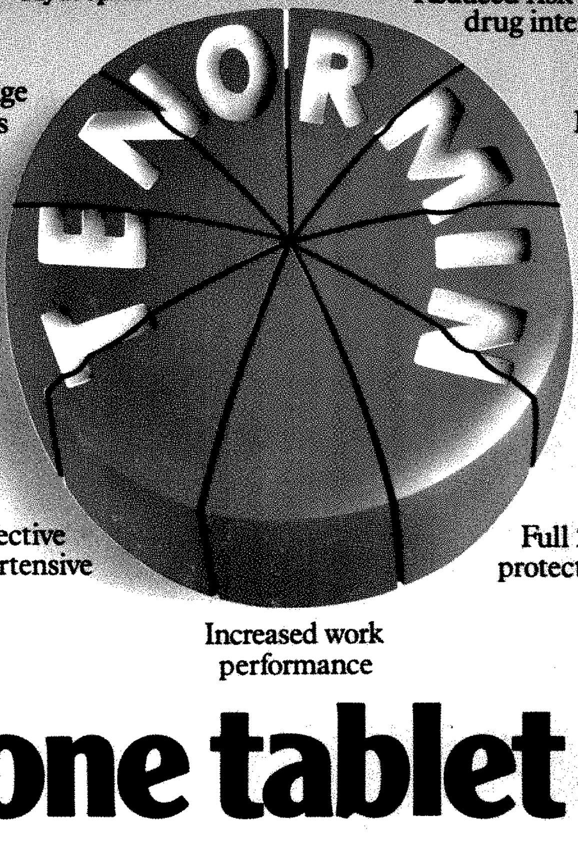

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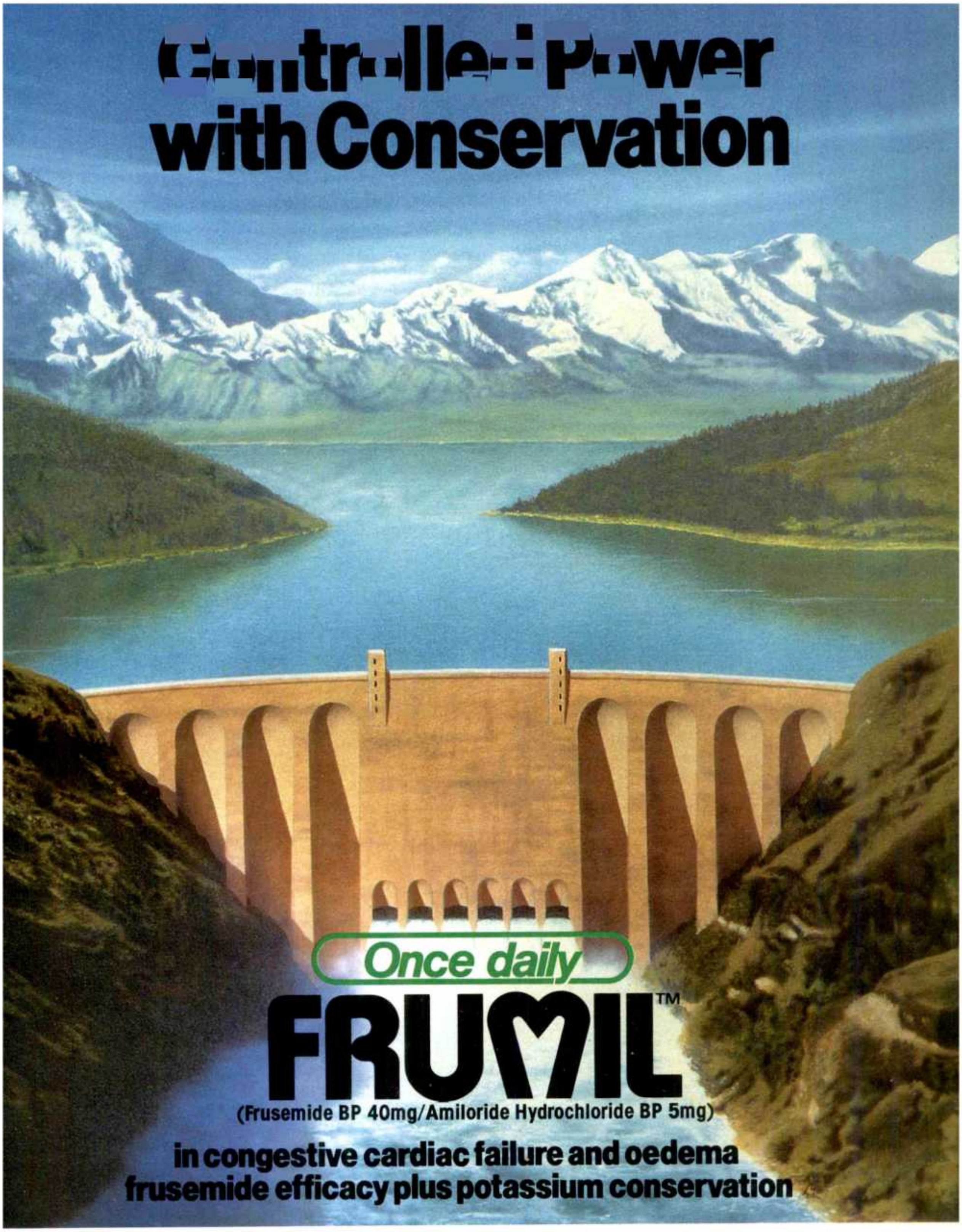
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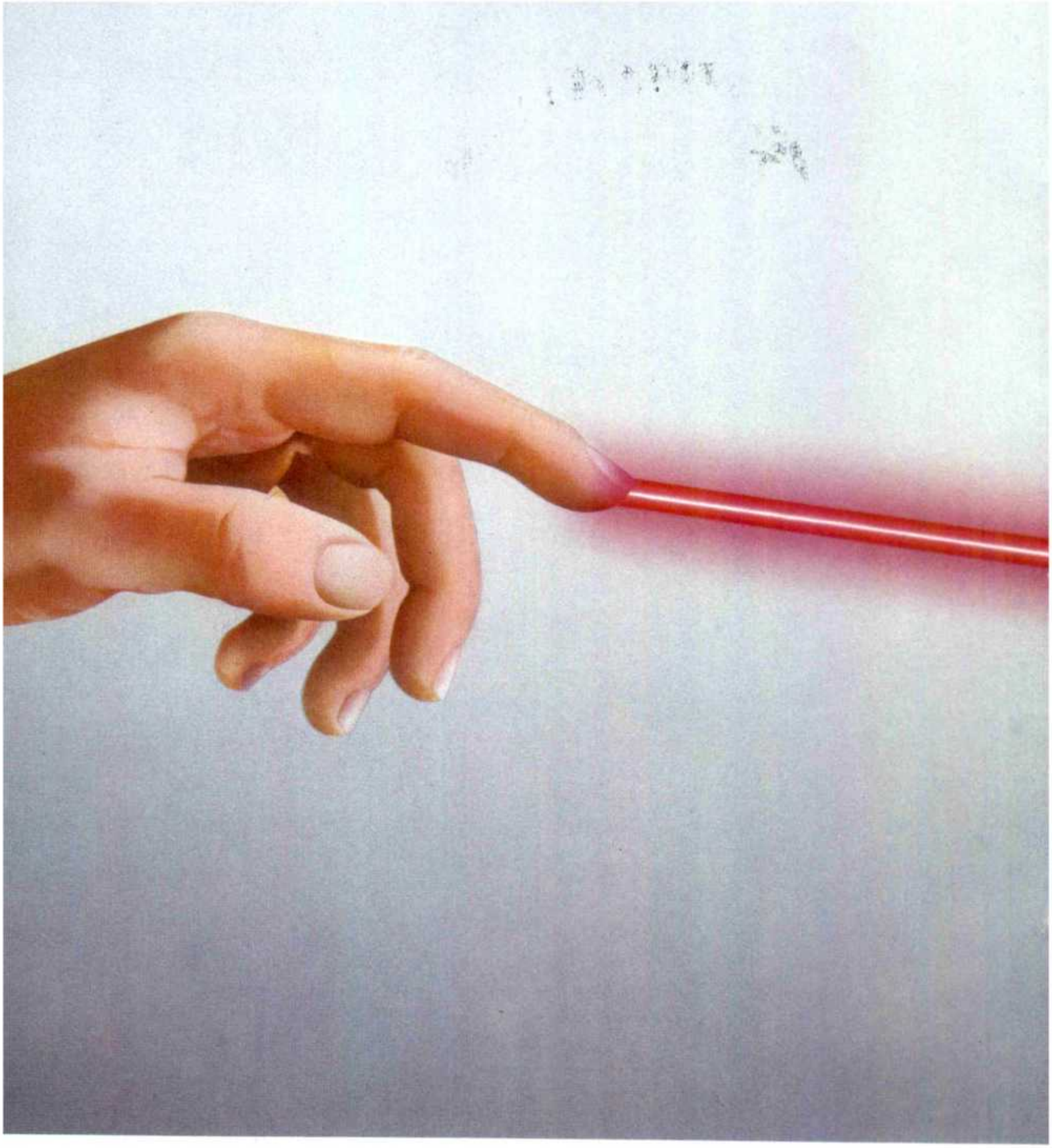

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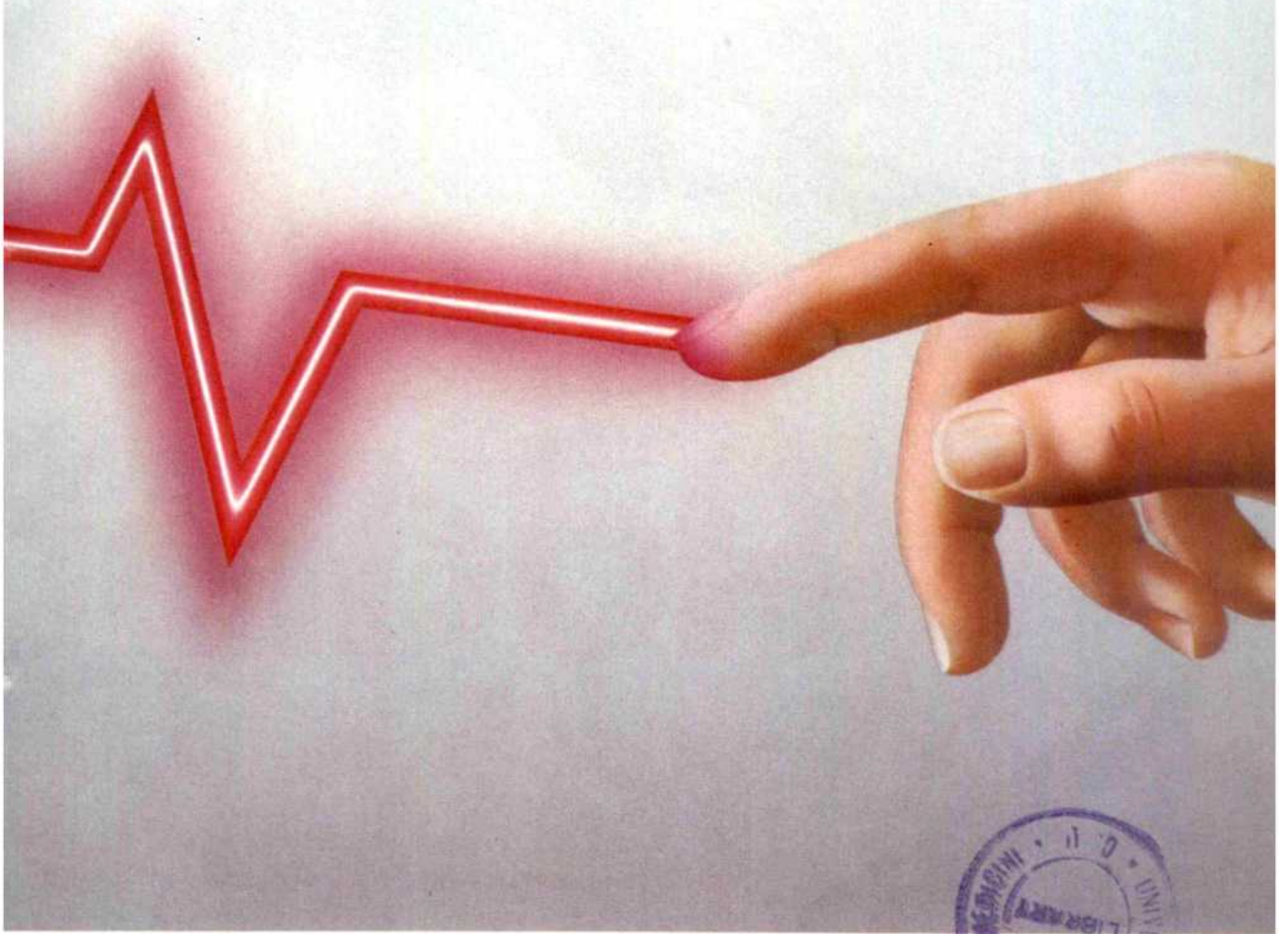

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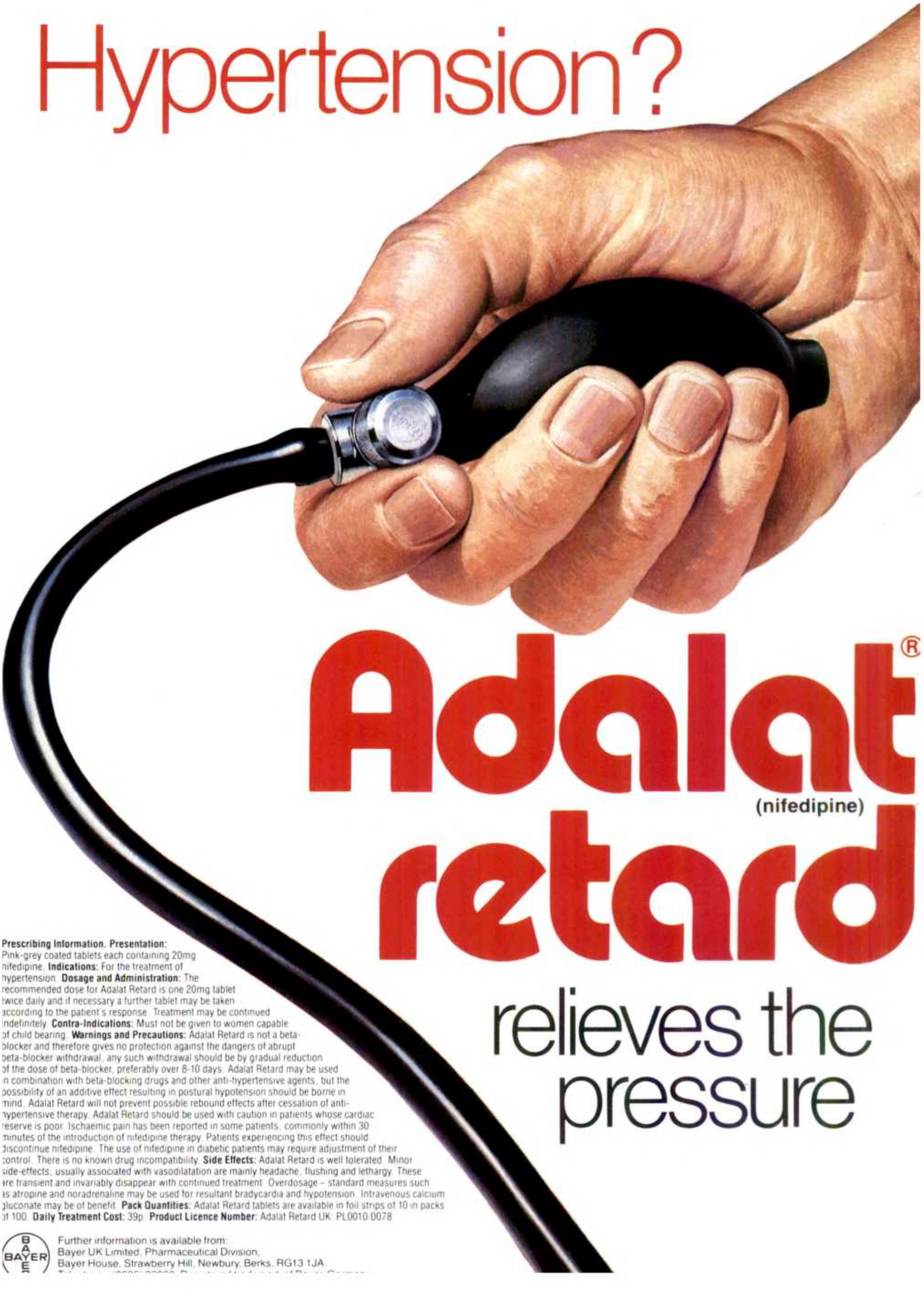

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Br Heart J 1985; **53**: 237–9

Editorial

Coronary artery bypass grafting and hyperlipidaemia

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The widespread introduction of saphenous vein grafting to bypass atheromatous lesions of the coronary arteries over 15 years ago[1] has had a profound effect on the management of ischaemic heart disease. It has been estimated that 65 000 such procedures were carried out in the United States of America during 1975,[2] and the annual rate has probably risen appreciably during the subsequent decade. The benefits of coronary artery bypass grafting have been the subject of much debate, but there is now increasing evidence that this procedure not only relieves symptoms but also increases longevity.[3]

Need for grafting in hyperlipidaemic patients

Numerous studies have shown a relation between the severity of angiographically assessed coronary artery disease and hyperlipidaemia,[4–14] as judged by the age of onset of symptoms,[4 7] the multiplicity of vessels involved,[5 7] and the tendency for lesions to progress.[6 10] Angiographic abnormalities are associated more closely with hypercholesterolaemia than with hypertriglyceridaemia[7 9 12] and correlate inversely with the ratio between high density lipoprotein (HDL) cholesterol, especially its HDL_2 subfraction, and low density lipoprotein (LDL) cholesterol.[13] Increases in LDL cholesterol and decreases in HDL cholesterol are each independently associated with the severity of disease[14] and often occur together in patients with type II hyperlipoproteinaemia, especially when this is due to familial hypercholesterolaemia. Such individuals are known to have an especially high frequency of three vessel and left main stem disease.[15 16] In view of the evidence that coronary artery bypass grafting exerts its greatest impact on prognosis in just these categories of coronary artery disease,[17 18] this implies that the indications for carrying out this procedure will occur relatively more often in hypercholesterolaemic patients than in those with normal serum lipid concentrations. In individuals with the rare homozygous form of familial hypercholesterolaemia bypass grafts are performed prophylactically to minimise the hazards of the ostial stenosis to which they are so prone or as an accompaniment to the formidable procedure which involves excision of the atheromatous aortic valve, enlargement of the aortic annulus, and insertion of a Björk-Shiley prosthesis.[19]

Effect of hyperlipidaemia on saphenous vein grafts

An early study[20] suggested that grafts patent at two weeks occluded more frequently during the subsequent year in patients whose serum triglyceride concentrations were raised preoperatively or postoperatively than in those with normal values. This was attributed to the fact that hypertriglyceridaemia tends to be associated with hypercoagulability, as was confirmed recently,[21] thus predisposing to early thrombotic occlusion. Histological studies of grafts obtained at the time of reoperation or necropsy several years after the initial procedure showed atheromatous changes which were largely confined to individuals who remained hyperlipidaemic postoperatively.[22 23] A similar but larger study showed a five fold increase in the incidence of vein graft atheroma in hyperlipidaemic compared with normolipidaemic individuals dying 1–5 years after coronary artery bypass grafting.[24]

Recently, three angiographic studies with varying periods of follow up have been reported. The largest but shortest study found that the majority of grafts patent at one year were unchanged three years after operation.[25] Progression of disease in grafts was evident in only 11% of 221 patients and was unrelated to serum cholesterol concentration. Nevertheless, a longer study showed progressive narrowing in 44% of grafts by five years, especially in hyperlipidaemic

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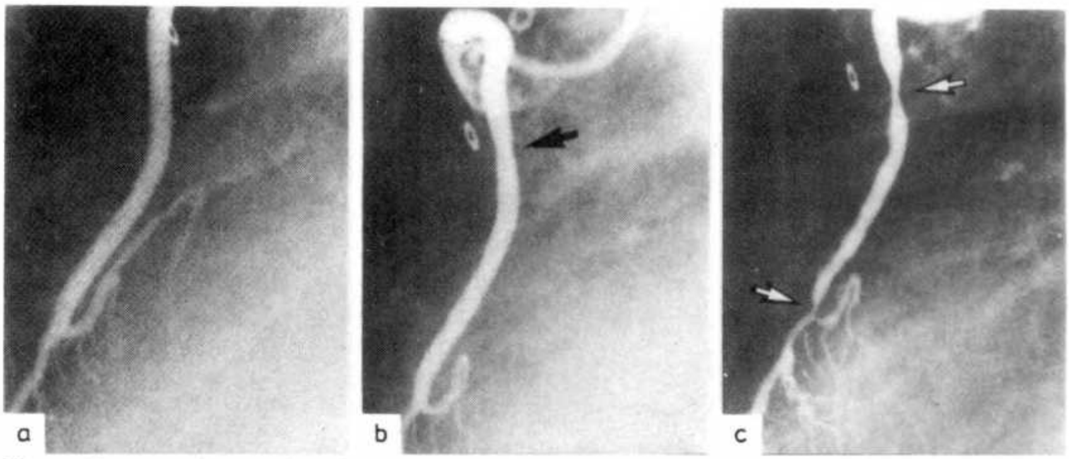

Figure *Coronary angiograms of a saphenous vein graft to the left anterior descending artery showing (a) normal appearance at one year, (b) minimal narrowing at six years (black arrow), and (c) severe stenoses at 10 years (white arrows). (Source: Campeau et al[27] by permission of the American Heart Association, Inc.)*

patients.[26] The longest follow up to date has been reported by Campeau *et al.*[27] Of 132 grafts shown to be patent at 6–18 months, 38% were unchanged at 10–12 years, 32% had changes suggestive of atherosclerosis (Figure), and 30% had completely occluded. The annual occlusion rate was 2·1% during the first five years and 5·2% thereafter. Concentrations of LDL cholesterol and LDL-apoB, the significance of which has been discussed recently,[28] were higher and HDL cholesterol concentrations were lower in patients with graft atherosclerosis than in those without.[29] The functional consequences of late graft closure are emphasised in a recent report which shows that the beneficial effect of coronary artery bypass grafting on longevity is demonstrable at seven years but not after 11 years of follow up.[30]

Effects of treatment

Data on the effects of treatment on graft patency are scanty and sometimes conflicting. Pantely *et al* reported the failure of antiplatelet or anticoagulant treatment to influence graft patency during the first six months after grafting[31] but two subsequent studies showed that dipyridamole combined with a high dose of aspirin[32] or a low dose of aspirin given alone[33] significantly improved graft patency during the first postoperative year. Whether treatment of hyperlipidaemia exerts any beneficial effects on graft survival remains to be established. The recently reported National Heart, Lung and Blood Institute type II intervention trial suggests that reducing LDL cholesterol and increasing HDL cholesterol concentrations by cholestyramine retards the progression of established disease in native vessels,[34 35] and it seems probable that a similar effect could occur in vein grafts. If this is not the case then the likelihood is that a high proportion of hyperlipidaemic patients will require further surgery within 10 years of first receiving a graft, with all the risks and expense that this entails. For the present it would seem sensible to give antiplatelet treatment to all patients for at least a year postoperatively and to identify and treat hyperlipidaemia on a long term basis.

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Intracardiac contrast echoes during transvenous His bundle ablation

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From the Cardiovascular Unit, Hammersmith Hospital, London

SUMMARY Two patients undergoing endocavitary ablation for resistant supraventricular tachycardia had cross sectional echocardiography performed during the ablative procedure. In both cases immediate opacification of the right heart cavities occurred at the time of the current discharge. The contrast effect was similar to that resulting from a peripheral venous injection of dextrose or saline during echocardiography for the diagnosis of intracardiac shunts. In one patient contrast echoes were also seen in the left ventricle. This contrast effect may be produced by gaseous release or blood element destruction. The risk of embolisation in patients undergoing endocavitary ablation, particularly on the left side of the heart, should be further evaluated.

Endocavitary ablation has recently been used in the control of resistant supraventricular arrhythmias.[1] DC discharge with energies of up to 500 J are delivered to the right side of the ventricular septum via a transvenous pacing electrode. Complete heart block is thereby induced by destruction of the atrioventricular node-His bundle or tissue in the region of this structure.[1 2] This procedure has also been advocated for the ablation of local regions of left or right ventricular myocardium, identified electrophysiologically to be responsible for ventricular tachycardia.[3]

The energies produced by this current discharge result in a transient rise in temperature and pressure[4] with presumably additional electrolytic effects. One or more of these effects may be responsible for the local destruction of myocardial or conducting system tissue. The changes that these transient physical alterations induce in blood within the ventricular cavities may include gaseous release or blood element destruction. If produced by current discharge, small particles may therefore represent a potential risk for embolism to the small vessels of the pulmonary or systemic circulation.

Cross sectional echocardiography has been previously used to detect contrast echoes when small particles—in this case gas bubbles produced by systemic venous injection—follow abnormal intracardiac blood flow patterns in conditions such as atrial septal defect.[5] We report the use of cross sectional echocardiography to characterise the effect of endocavitary current discharge on the intracardiac blood pool in two patients undergoing His bundle ablation.

Patients and methods

Two patients, aged 38 years (case 1) and 43 years (case 2), underwent His bundle ablation because of symptomatic paroxysmal atrial fibrillation which had proved unresponsive to medical treatment. Neither patient had identifiable structural heart disease, and at the time of study the foramen ovale was considered closed. Under general anaesthesia and with muscle relaxation a standard temporary transvenous electrode (USCI 6F Tripolar) was introduced into the right ventricle via the femoral vein. The electrode was positioned adjacent to the His bundle so that a stable unipolar His bundle electrogram of at least 0·25 mV was recorded. A total of six DC discharges (five for case 1, one for case 2) were delivered between the intracavitary electrode and a back plate, used as the cathode. The discharge was timed to the R wave of the electrocardiogram; thus it occurred when the tricuspid valve was open. One DC discharge (case 1) was of 20 J and the remainder (for both patients) were of 320 J. In both patients permanent complete heart block was produced and the cardiac rhythm

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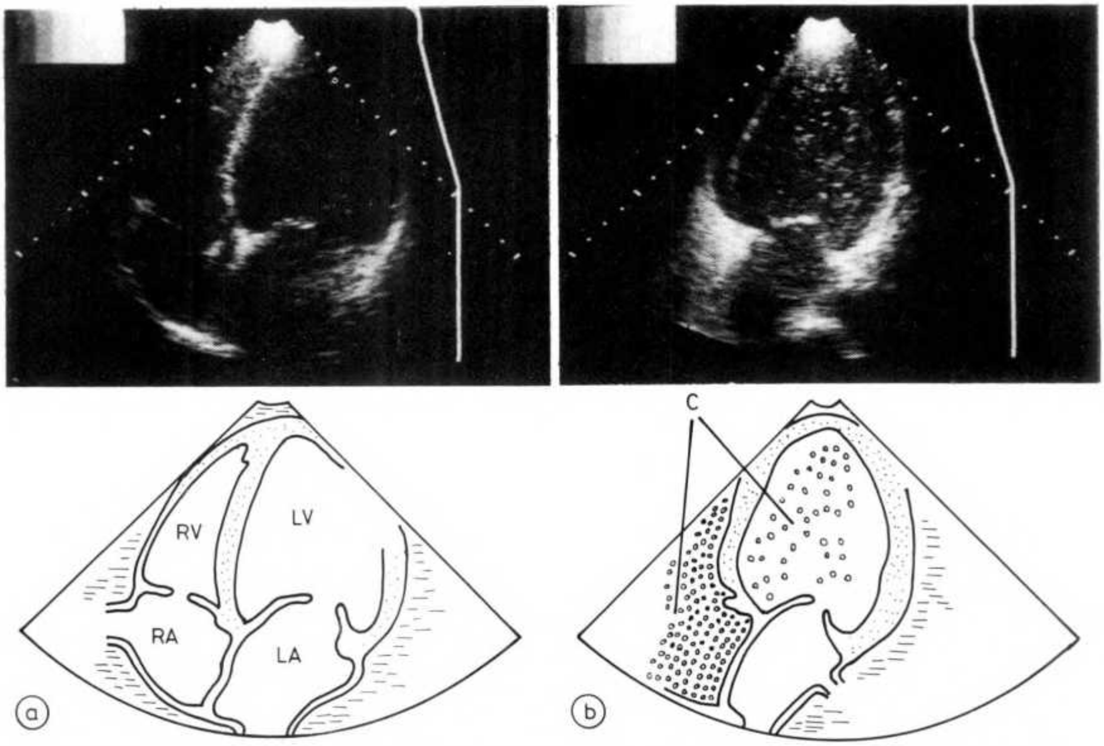

Figure *Cross sectional echocardiograms of the heart in the apical four chamber view (case 2), (a) immediately before current discharge and (b) after current discharge showing dense opacification of the right heart and to a lesser extent the left ventricle. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; C, contrast.*

immediately supported by temporary ventricular pacing and later by the insertion of a permanent pacemaker.

Cross sectional echocardiograms of the left and right heart chambers were recorded from an apical four chamber view throughout the procedure. Both the operator and system were electrically isolated from the current discharge. The presence and intensity of contrast echoes produced by DC discharge and the time course for their resolution were noted.

Results

Immediately after each DC discharge, profound opacification of the right ventricular and atrial cavities was seen (Figure). This contrast effect cleared only after several heart beats and occurred whether or not complete heart block resulted from the discharge. The intensity of this echo effect was subjectively judged as less for the one DC discharge which used 20 J.

In the patient in case 2, the DC discharge produced an additional, although less intense, contrast effect within the left ventricle. The passage of contrast echoes through a patent foramen ovale cannot be excluded on the basis of one observation; nevertheless, this appeared unlikely as the echoes appeared at the same time within the left and right ventricles during temporary atrial and ventricular asystole and were not seen within the left atrium. For the same reasons, the left ventricular echoes did not appear to have traversed the pulmonary circulation and thus presumably arose from transfer of the physical effect of the discharge across the ventricular septum adjacent to the ablated region.

During the asystolic period after the DC discharge in the patient in case 2, additional but qualitatively different contrast echoes appeared within the left ventricle. These were similar to echoes generated with current high resolution echocardiographic systems when intracardiac stasis occurs such as in the left atrium in severe mitral stenosis. A clinical evaluation of each patient after the procedure showed no evidence of pulmonary or systemic embolism.

Discussion

We noted contrast echoes within the cardiac chambers after DC discharge via a right ventricular electrode when His bundle ablation was attempted. The density of echoes produced, particularly at higher current energies, obliterated the right heart chambers for several seconds after current discharge before being cleared to the pulmonary circulation. Although echo density was greatly enhanced, the echoes appeared to be qualitatively similar to those used when performing diagnostic contrast echocardiographic studies. It is, therefore, likely that they originated from similar sized ultrasonic target particles (approximately 15–30 μ in diameter). Gaseous particles dissociated from solution by DC induced electrolysis may cause this effect, a view supported by our observations of small bubble clouds in the region of an electrode when discharged in a saline bath. Nevertheless, current discharge may also produce small solid particles as a result of destruction and aggregation of blood elements.

Although the exact nature of this phenomenon is unclear, the pronounced contrast echo effect indicates a potential risk of embolisation. No major pulmonary embolic complications have been reported with right sided ablation procedures despite considerable experience with the method. While this is no doubt due to the small size and possible gaseous nature of the particles produced, the effect and risk of embolism in small pulmonary vessels from these particles need to be determined.

Contrast echoes, whatever their nature or origin, produced in the left ventricle represent a more serious risk in that systemic embolism may occur. The long term sequelae of small particle emboli after cardiopulmonary bypass are being increasingly considered.[6] Gaseous particles produced after endocavitary ablation, and particularly in quantity if large current energies need to be used, might constitute a similar risk to the small vessel circulation of the brain or other organs. This risk may further be increased if solid aggregates contribute to the contrast effect. Although experience with left sided intracavitary ablation is less than with right sided procedures, major embolism has not been reported. Small vessel effects, however, may not be obvious on clinical grounds, and more sensitive investigations may be necessary to determine whether small vessel organ damage has occurred. Specific studies concerning the nature of contrast effect, its relation to current energies used, and the embolic potential of left sided current discharge in an animal model may answer some of the questions raised by our observations.

Although major embolism has not been reported in the early experience of His bundle ablation, our findings suggest that the risks of adverse effect on the pulmonary and especially the systemic circulation should be considered before similar techniques gain widespread acceptance, particularly in the treatment of left ventricular tachycardia.

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Long term survival of patients mobilised early after acute myocardial infarction

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SUMMARY A Welsh multicentre trial of early (fifth day) compared with late (tenth day) mobilisation in 742 patients after uncomplicated myocardial infarction, reported previously, found that there were no significant differences in survival during the first year, but a partial follow up beyond the first year survival showed a significantly reduced survival during the second and third years among patients mobilised early. A full 10 year follow up of all patients admitted to the trial was therefore carried out. A small difference in survival was confirmed, which reached about 5% at four years; but the difference was not statistically significant. Further analysis suggested the possibility of real differences in survival in certain subgroups, but the present evidence was not sufficient to provide contraindication to mobilisation five days after uncomplicated myocardial infarction.

Since Levine and Lown advocated armchair treatment for patients with acute coronary thrombosis[1] there has been a progressive reduction in the average duration of bed rest. There have been several randomised trials of duration of bed rest and duration of stay in hospital (cited in [2]). In the previously reported Welsh multicentre trial of early mobilisation after uncomplicated acute myocardial infarction 742 patients were randomised to five days or to 10 days of bed rest. The early and late mobilisation groups were comparable, and no significant differences in mortality or in morbidity in the first year were found.[2] Similar smaller trials have shown no disadvantage of early mobilisation either in mortality or in morbidity during shorter follow up periods, usually of six weeks to six months (cited in [2]). In our Welsh trial, however, follow up information was available for some patients beyond one year, because the intended one year follow up was inadvertently delayed. An unexpected finding from that incomplete late follow up was that the survival rates of the two groups diverged during the second and third years after trial entry, with those mobilised early having significantly higher mortality. The finding has given rise to some concern about the advisability of early mobilisation.[3] We report the full follow up data eight to 10 years after admission to the trial.

Patients and methods

The original trial comprised 742 patients aged <70 years with uncomplicated acute myocardial infarction in 1973–74 in 12 district general hospitals throughout Wales under the care of 31 consultants, mobilised on either the fifth or the tenth day after the onset of pain. Acute myocardial infarction was defined on typical clinical features, electrocardiographic evidence of probable infarction (World Health Organisation criteria[4]), and serum enzyme activities of twice the laboratory normal value. Complications that prevented inclusion were at the discretion of the consultant, although guidelines of such complications were included in the trial protocol. Information on patient identification, brief medical history, and brief clinical findings were recorded on the day of admission (generally the same as the day of onset of pain, which was defined as day 0) and brief clinical findings were recorded again on day 5 (the day of randomisation and admission to the trial) and again on day 10. Comparable information was collected similarly for patients with complicated acute myocardial infarction on day 5 who were excluded from the trial. Guidelines were provided for gradually increasing activity after mobilisation, necessarily allowing some variation from hospital to hospital and from patient to patient. It was recommended that patients be discharged home one week after mobilisation. Patients were reviewed at between six and 36 months after admission to the trial. The results of mortality and morbidity in the first year have been reported previously.[2]

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In this further follow up study all patients admitted to the trial were traced to ascertain vital information via hospital, general practitioner, home address, the Office of Population Censuses and Surveys (OPCS), and the NHS Central Register, and then again via Family Practitioner Committee, general practitioner, and home address. Copies of death certificates of the deceased were obtained from the OPCS. The follow up was undertaken during March to September 1983, and survival up to eight to 10 years, depending on the date of admission (1973–4), was calculated by life table methods.[5] Survival between patients mobilised on day 5 and those mobilised on day 10 was compared by the Mantel Haenszel (logrank) test.[6] Further comparisons of survival by age, sex, hospital, previously recorded medical history, and clinical findings on admission were similarly made by the Mantel Haenszel test. The causes of death were compared by age, duration of survival, and mobilisation group.

The numbers of patients admitted to the two groups differed slightly; 348 were mobilised on day 5 and 394 on day 10. This degree of inequality is not significant: the limits are 343 and 399 (at $2\alpha=0{\cdot}05$). Much of the inequality was contributed by two consultants, who admitted 8 and 23 and 14 and 23 patients on days 5 and 10 respectively. The former inequality is significant (limits 9 and 22) while the latter is not (limits 12 and 25). Since the inequality for the trial as a whole was not significant and since there were 31 consultants it is quite possible that a "significant" inequality could have occurred by chance for one. Nevertheless, in case there should have been any selection bias all survival calculations were reworked excluding (*a*) the 31 patients admitted by the one consultant and (*b*) the further 37 patients admitted by the other consultant.

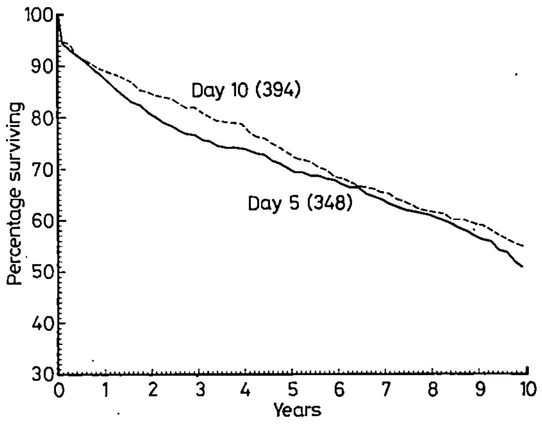

Fig. 1 *Survival by day of mobilisation (day 5 or day 10). Figures in parentheses are numbers of patients.*

Results

OVERALL SURVIVAL

Figure 1 shows the survival curves of patients mobilised on day 5 and those mobilised on day 10 after uncomplicated acute myocardial infarction. One year after admission to the Welsh multicentre trial 88% of those mobilised early and 89% of those mobilised late survived: the first year survivals were not statistically different.[2] During the second to sixth years the survival of those mobilised early appeared to be somewhat lower than for those mobilised late, with a maximum apparent difference of 5% at four years. The difference was not, however, statistically significant (Mantel Haenszel logrank 0–4 y $\chi^2=2{\cdot}3$ and $p\approx0{\cdot}13$). The survival rates were more similar over the seventh to ninth years but separated again in the final year. Ten years after admission to the trial 51% of those mobilised early and 55% of those mobilised late survived: the overall 0–10 years difference was not statistically significant. Of all 742 patients, 16 were lost to follow up before eight years and 38 and 172 were "right censored" during the ninth and tenth years respectively. The overall survival rate after 10 years was 53%. The mortality rate in the first year was 11% and the annual mortality rate after the first year 4%.

SURVIVAL IN SUBGROUPS

The survivals of patients mobilised on day 5 and on day 10 were compared in various subgroups (by age, sex, hospital, previous medical history, and clinical findings on admission) to look for an explanation for the apparent separation of the curves, particularly in the second to sixth years. The Table summarises the results at four years, the centre of the separation, and at 10 years. Several subgroups showed a higher mortality from about one year after infarction in the early mobilisation group: (*a*) patients admitted to hospital F, (n=110, Mantel Haenszel 0–4 yr, $p<0{\cdot}05$), (*b*) patients with previous history of hypertension (n=83, Fig. 2a, $p<0{\cdot}05$), (*c*) patients with arrhythmia on admission (n=137, Fig. 2b, $p<0{\cdot}01$), and (*d*) patients with bradycardia on admission (heart rate <60 beats/min, n=58, Fig. 2c, $p<0{\cdot}02$). Most of these differences were at their greatest about four years after trial entry. For patients with a previous history of angina and for those with hypotension on admission the apparent differences were not significant. The differences in the opposite sense at four years (apparently lower mortality among those mobilised early) among patients admitted to hospital C and among the relatively few patients who had histories of previous myocardial infarction or who had tachycardia on admission were all not significant. All long term survival calculations were repeated excluding the contributions of the two consultants who entered excess patients into the late mobilisation

Table *Analysis of survival by subgroup*

	No of patients		*Survival at four years*		*Survival at 10 years*	
	Day 5	*Day 10*	*Day 5*	*Day 10*	*Day 5*	*Day 10*
Age (yr):						
≤44	44	44	0·81	0·86	0·69	0·71
45–54	116	124	0·78	0·81	0·58	0·62
55–64	144	160	0·74	0·80	0·43	0·52
≥65	44	66	0·57	0·67	0·38	0·38
Sex:						
Male	301	330	0·73	0·78	0·48	0·54
Female	47	64	0·83	0·84	0·65	0·54
Hospital:						
A	59	63	0·68	0·79	0·36	0·54
B	49	54	0·75	0·78	0·43	0·58
C	49	52	0·82	0·67	0·68	0·47
D	39	45	0·87	0·77	0·49	0·51
E	32	54	0·75	0·81	0·52	0·60
F	54	56	0·69	0·88	0·59	0·62
Six others	66	70	0·68	0·80	0·45	0·52
History of:						
Acute myocardial infarction	10	8	0·70	0·50	0·40	0·38
Angina	90	126	0·60	0·68	0·32	0·48
Hypertension	29	54	0·48	0·72	0·34	0·44
Risk features:						
BP≥180 mm Hg	51	59	0·76	0·71	0·43	0·44
BP<120 mm Hg	47	64	0·70	0·82	0·53	0·65
HR≥120 beats/min	24	14	0·63	0·43	0·21	0·21
HR<60 beats/min	18	40	0·72	0·95	0·65	0·68
Arrhythmia:	55	82	0·67	0·87	0·45	0·57
Severe cardiac pain	47	70	0·74	0·75	0·58	0·47
Severe dyspnoea	15	13	0·47	0·46	0·20	0·21
All patients	348	394	0·74	0·79	0·51	0·55

BP, blood pressure; HR, heart rate.

group. For both of them the survival rates of the relatively few patients entered into the early mobilisation group were unusually favourable, which suggests possible bias. Exclusion of these data accordingly resulted in a widening of the difference in survival in the trial but not to the point of significance (Mantel Haenszel 0–4 y, $p \approx 0{\cdot}08$). Survivals were compared also in the subgroups after exclusion of the data from these two consultants, and these exclusions also resulted in widening of the differences but not enough to change the levels of significance.

LONG TERM SURVIVAL

The long term survivals by age of patients admitted to hospital for acute myocardial infarction, who were alive and uncomplicated on the fifth day after the onset of cardiac pain, are summarised by pooling the results of early and late mobilisation groups (Fig. 3). After 10 years 70% of patients age ≤44, 60% of those aged 45–54, 48% of those aged 55–64, and 38% of those aged 65–69 were still living. Only 18 patients admitted to the trial had experienced previous acute myocardial infarction, and their 10 year survival was 39% (not significantly lower than the 53% for the trial as a whole owing to the small numbers). Two hundred and sixteen patients had previous angina with a 10 year survival of 41% ($p \leq 0{\cdot}0001$), and 83 had histories of hypertension with a 10 year survival of 41% ($p<0{\cdot}01$). Of the potential "risk features" on admission to hospital, tachycardia (heart rate ≥120 beats/min) conferred a lower than average survival (21% survival at 10 years, $p<0{\cdot}001$) and so did severe dyspnoea (24% survival at 10 years, $p<0{\cdot}01$).

CAUSES OF DEATH

The causes of death (Ic, Ib, or Ia on the death certificate) were described as (*a*) heart disease (ICD 410–414) 71%, (*b*) other circulatory diseases (ICD 390–405 and 415–459) 18% (mostly hypertension, cerebrovascular disease, and arteriosclerosis), and (*c*) other causes 11% (mostly cancer). There were slightly more deaths from heart disease and fewer from other circulatory diseases among patients mobilised early: 74% and 16% respectively for day 5 compared with 68% and 19% for day 10, but these differences were not statistically significant. There were fewer deaths from heart disease and more from other causes (group *c*) in old patients; 59% and 20% respectively of those aged over 65 ($p<0{\cdot}05$). There were more deaths due to heart disease during the first year (84%) and more deaths from other circulatory disease (22%) and other causes (14%) during the second to sixth years ($p<0{\cdot}02$).

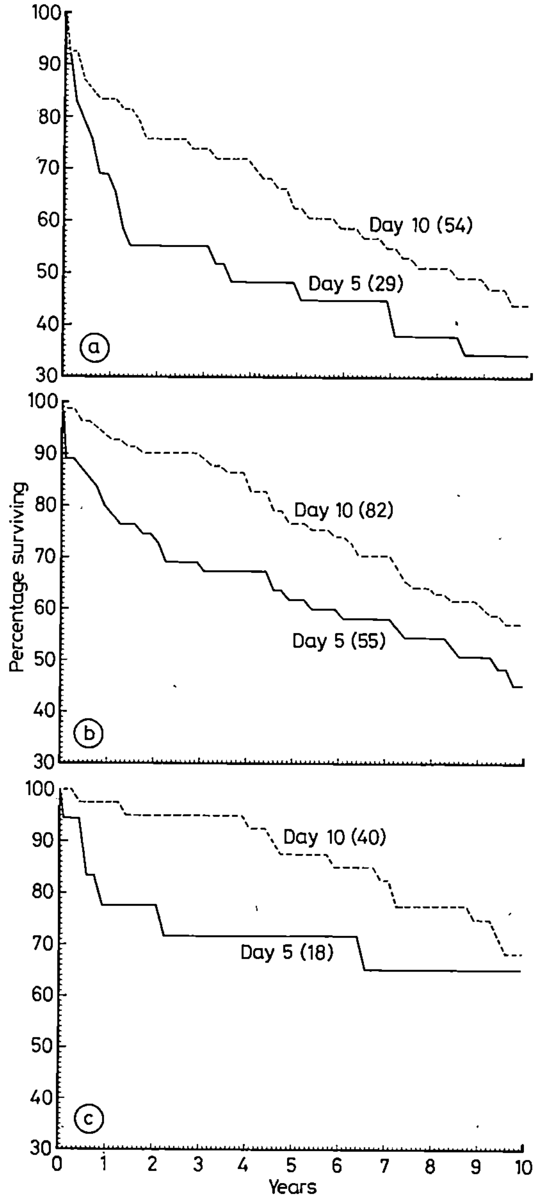

Fig. 2 *Survival of patients (a) previously treated for hypertension, (b) with arrhythmias on admission, and (c) with bradycardia on admission according to day of mobilisation. Figures in parentheses are numbers of patients.*

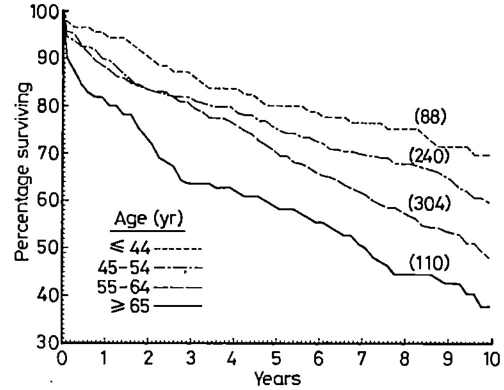

Fig. 3 *Survival by age group. Figures in parentheses are numbers of patients.*

Discussion

This 10 year follow up of the Welsh multicentre trial of early mobilisation after uncomplicated myocardial infarction has shown that the lower survival after early mobilisation on the fifth day compared with late mobilisation on the tenth day that appeared during the partial 2–3 year follow up was not significant in the trial as a whole. A small non-significant difference in survival between the early and late mobilisation groups was confirmed, reaching a maximum of about 5% at four years. Subgroups of patients were identified with significantly lower survival after early mobilisation: patients admitted to hospital F, patients with a history of hypertension, and patients with bradycardia or arrhythmia on admission to hospital. Only the last two of these groups overlapped significantly; 28/137 with arrhythmia also had bradycardia.

Overall mortality after the fifth day for patients with uncomplicated myocardial infarction was 11% in the first year and approximately 4% a year thereafter. This is marginally less than previously reported mortality rates after acute myocardial infarction, although close comparisons are not possible because of differences between series.[7–12] It also compares quite favourably with the expected mortality of about 2% in the normal population of the same sex and age distribution.[13]

The early and late mobilisation groups were generally comparable. During the trial all participating centres were visited periodically (by RRW), and the trial protocol was described to new house officers when appointed. Patient admissions were monitored centrally: deviations from the prenumbered sequence of randomisation cards were noted and the numbers of trial inclusions were compared with Hospital Activities Analysis (HAA) records of admissions for each consultant. Participating centres were sent progress reports and were questioned regarding any deviations from the prenumbered sequence, incomplete forms, or unusually low proportions of admissions to the trial. The non-significant excess of patients mobilised late has been shown to be attributable to entries on behalf of two of the 31 participating consultants. Exclusion of data from these sources resulted in a slight widening of the differences in survival but not to the point of significance.

The significantly lower survival after early mobilisation in four of the 23 subgroups compared in the Table, the levels of significance of the survival differences, and the heightening of the differences after exclusion of data from the two consultants whose distribution of admitted patients showed possible bias taken together suggest that the differences may be more than a random consequence of multiple comparisons. It is possible that there is a small but "real" disadvantage of early mobilisation in terms of late survival, which could achieve statistical significance only in future larger trials. The overall difference, however, was maximal at four years, whereas a "real" difference might have been expected to be maximal during the first year when mortality is highest. Furthermore, the features distinguishing three of those subgroups apparently disadvantaged by early mobilisation do not obviously identify any clinical characteristics that might reasonably be considered as potential hazards: of the four subgroups, only hypertension was associated with reduced survival in the trial as a whole. The overall difference was at no time large. We believe that the evidence is not sufficient to contraindicate mobilisation as early as the fifth day after uncomplicated myocardial infarction.

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Limitations of a QRS scoring system to assess left ventricular function and prognosis at hospital discharge after myocardial infarction

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SUMMARY The value of a QRS scoring system derived from 12 lead electrocardiograms to estimate left ventricular ejection fraction was assessed in a prospective study of 285 hospital survivors of myocardial infarction. In these patients both the QRS score and ejection fraction were measured by radionuclide ventriculography at discharge. The correlation between ejection fraction and QRS score was weak. In 22 patients who died during six to 12 months follow up the ability of the ejection fraction and QRS score to predict mortality was assessed in terms of sensitivity, specificity, predictive value of a positive and negative test, and efficiency. For ejection fraction <40% and a QRS score ≥6 sensitivity was respectively 73% and 64%, specificity 73% and 56%, predictive value of a positive test 18% and 11%, predictive value of a negative test 97% and 95%, and efficiency 73% and 56%.

Both ejection fraction and QRS score may be used to identify patients at low and high risk during one year follow up, but, contrary to initial expectations, the QRS score appears to be of little value in estimating ejection fraction and is less accurate than ejection fraction in predicting late survival in hospital survivors of myocardial infarction.

The 12 lead electrocardiogram is widely used to diagnose and follow up patients after myocardial infarction. It is inexpensive and non-invasive and therefore easily repeatable. Since the direct measurement of left ventricular function has been shown to be a major determinant of prognosis in such patients,[1] the recent introduction by Wagner *et al*,[2] Ideker *et al*,[3] and Roark *et al*[4] of a weighted QRS score which showed a good correlation with infarct size and left ventricular ejection fraction[5 6] has attracted considerable interest.[7–9] Furthermore, the QRS score was shown to be useful for predicting hospital as well as late mortality afer myocardial infarction.[6–10] These optimistic expectations from the original studies have been tempered by some subsequent reports[7–9] which found a weak correlation between Wagner's QRS score and left ventricular ejection fraction. Young *et al*[9] found an even weaker correlation between ejection fraction and other electrocardiographic scores such as described by Askenazi *et al*,[11] Gottwik *et al*,[12] and Rautaharju *et al*.[13] In the light of this controversy, the value of the QRS score described by Wagner *et al*[2] was prospectively reassessed for determining left ventricular ejection fraction and predicting late survival in 285 hospital survivors of myocardial infarction.

Patients and methods

Two hundred and eighty seven hospital survivors of acute myocardial infarction who were admitted to a coronary care unit between 1 March 1981 and 31 January 1983 formed the data base for this study. During this period there were 422 potential candidates (hospital survivors of acute myocardial infarction); 57 were excluded because the electrocardiographic score could not be computed (nine had complete left bundle branch block, 20 complete right

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Table 1 *Explanation of QRS scoring system*[2]

ECG lead	*Q wave duration (ms)*	*R wave duration (ms)*	*Amplitude ratios*	*Points*	*Maximum*
I	≥30	—	—	1	—
	—	—	R:Q≤1	1	2
II	≥40	—	—	2	—
	≥30	—	—	1	2
aVL	≥30	—	—	1	—
	—	—	R:Q≤1	1	2
aVF	≥50	—	—	3	—
	≥40	—	—	2	—
	≥30	—	—	1	—
	—	—	R:Q≤1	2	—
	—	—	R:Q≤2	1	5
V1	Any	—	—	1	—
	—	≥50	—	2	—
	—	≥40	—	1	—
	—	—	R:Q≥1	1	4
V2	Any or	≤20	—	1	—
		≥60	—	2	—
		≥50	—	1	—
		—	R:S≥1·5	1	4
V3	Any or	≤30	—	1	1
	≥20	—	—	1	—
	—	—	R:Q or R:S≤0·5	2	—
V4	—	—	R:Q or R:S≤1·5	1	3
V5	≥30	—	—	1	—
	—	—	R:Q or R:S≤1	2	—
	—	—	R:Q or R:S≤3	1	3
V6	≥30	—	—	1	—
	—	—	R:Q or R:S≤1	2	—
	—	—	R:Q or R:S≤3	1	3

bundle branch block, 21 left superior fascicular block, five left inferior fascicular block, two pre-excitation, and two ventricular hypertrophy) and 78 were excluded because the ejection fraction measurement was unavailable. Myocardial infarction was diagnosed on the basis of at least two of the following conditions: typical history, classic electrocardiographic signs, and a diagnostic increase in serum enzyme activity.

For this group of 285 patients, the mean age was 57 (range 22–82) years, 82% were male, and 27% had a previous myocardial infarction. On admission 37% had an acute anterior myocardial infarction, 38% an inferior-posterior myocardial infarction, and 25% non-Q wave myocardial infarction; 74% were in Killip clinical class I. The median hospital stay was 13 (range 7–58) days.

To determine the QRS score, standard 12 lead electrocardiograms were obtained on a three channel Hewlett Packard 1513 A automatic cardiograph recorder at a paper speed of 25 mm/s on the day of hospital discharge or one day before. Conventional speed and sensitivity were used, because they are advocated for current clinical use. The QRS scoring system as described by Wagner *et al*[2] was applied (Table 1). The calculations were validated by the independent measurement of the score from a random sample of 39 electrocardiograms by the original author of the score, who was blinded to our measurements; the independent measurements showed no significant difference from the study readings (study score mean (SD) 4·8 (3·8) *vs* independent score 5·4 (3·9)). The correlation coefficient was 0·94 (SEE 1·3) with no apparent bias introduced.

Radionuclide ventriculography was performed at discharge in the 45° left anterior oblique view after in vivo labelling of the red blood cells with 555 MBq (15 mCi) of technetium-99 m. Acquistion was performed during a six minute period with a Searly Phogamma V camera (Siemens cardiac camera) equipped with a low energy all purpose-collimator.

The data were processed by a computer program with automated contour detection and correction for background activity. Left ventricular ejection fraction was computed from the end systolic and end diastolic images, as previously described.[14]

After hospital discharge all patients were followed at regular intervals. The median follow up was 10 (range 6–14) months. Mortality was the endpoint of interest in this study.

STATISTICAL ANALYSIS

Univariate analysis with Student's *t* test, χ^2 test, Fisher's exact test, or linear regression analysis were applied when appropriate. The most advantageous cutoff values to predict mortality were selected from visual inspection of the receiver-operator characteristic curves (ROC).[15] In these curves the specificity and sensitivity of the test are plotted, where sensitivity is

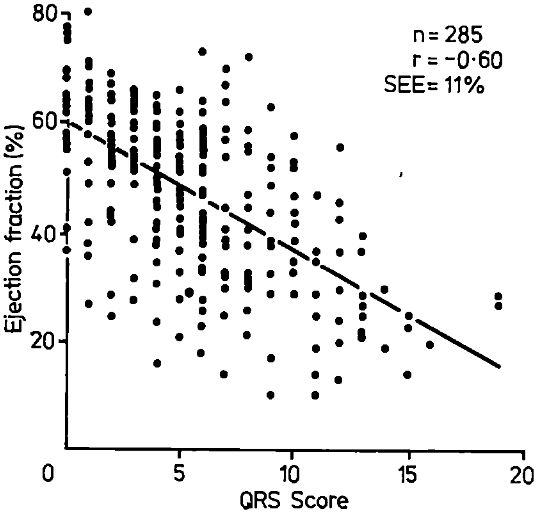

Fig. 1 *Correlation between radionuclide ejection fraction and QRS score.*

the fraction of correct classification of patients who satisfy the "endpoint" criteria, and specificity the fraction of correct classification of all patients who satisfy the "non-endpoint" criteria. These curves, when generated for different tests, provide a direct comparison of the various test results over the entire range of measurements. After selection of the most advantageous cutoff point for ejection fraction and the QRS score their relative accuracy to predict death was also determined in terms of predictive value of a positive test (true positives/all positive tests), predictive value of a negative test (true negative/all negative tests), and efficiency (true positives + true negatives/total population).

Results

Radionuclide ventriculograms and the QRS score were available in 285 patients. The correlation coefficient between the ejection fraction and QRS score in the entire group was −0·60 (SEE (standard error of the estimates) 11%) (Fig. 1). When patients with first infarction (n=202) are considered separately from those with previous infarction (n=83) the correlation was slightly stronger in the former group (r=−0·61 *vs* r=−0·48), but the dispersion of the data was just as large in the two groups (SEE 11%). The correlation between the ejection fraction and QRS score in patients with first anterior transmural infarction (r=−0·56) was similar to that in patients with first inferior infarction (r=−0·43) (Fig. 2) because of the equally large SEE (10%). Of 285 patients, there were 263 late survivors. Their ejection fraction was higher (48(14)% *vs* 35(16)%, p<0·001) and QRS score lower (5·4(3·7) *vs* 7·0(4·1), p=0·05) than in the 22 non-survivors. The visual inspection of the receiver-operator characteristic curves from radionuclide ventriculography and QRS score (Fig. 3) indicate that the ejection fraction had a superior predictive accuracy than the QRS score for late mortality. The "best" cutoff points—that is, the points with the highest sensitivity and the highest specificity—were 40% for ejection fraction and six for the QRS score. Survival and the other indices measuring the accuracy of the test to predict mortality by ejection fraction, QRS score, and the two tests combined are shown in Tables 2 and 3. They all indicate the superior accuracy of ejection fraction compared with the QRS score. The predictive accuracy was not improved by combining the

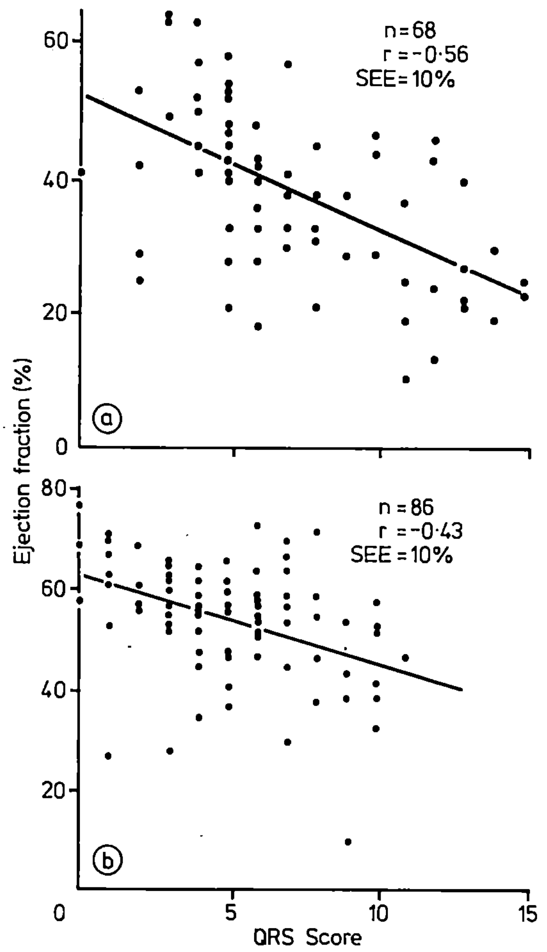

Fig. 2 *Correlation between radionuclide ejection fraction and QRS score in patients with (a) first anterior infarction and (b) first inferior infarction.*

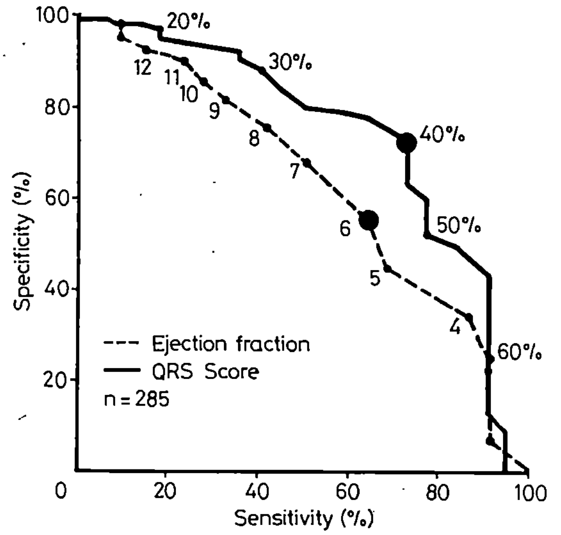

Fig. 3 *Receiver-operator characteristic curves of ejection fraction and QRS score for prediction of late mortality. During the entire range of measurements ejection fraction had a higher sensitivity than QRS score at comparable specificity to predict late mortality. The "best" cutoff points—that is, those with the highest sensitivity for the highest specificity—were 40% for ejection fraction and 6 for QRS score.*

ejection fraction and the QRS score, which, when compared with the ejection fraction alone, decreased the sensitivity while the other indices of predictive accuracy were unchanged.

Discussion

Several electrocardiographic indices have been reported to correlate with left ventricular function.[2 11–13 16] Nevertheless, in contrast to initial expectations based on small series of patients,[3 5] Young *et al* found in their review[9] that the correlation coefficient between ejection fraction and QRS score according to Wagner *et al*[2] was rather low (r=0·60). Because other authors also had similarly disappointing results,[7–9] they questioned the clinical usefulness of the QRS score for estimating ejection fraction in individual patients. We assessed the value of Wagner's score to estimate radionuclide left ventricular ejection fraction in a larger population as part of a continuing prospective study of patients after myocardial infarction. Our results corroborate those of Young *et al*[9] and de Pace *et al*,[7] who found a weak correlation between ejection fraction and QRS score in such patients (Table 4).

Table 3 *Indices of accuracy in predicting late mortality from radionuclide ejection fraction (EF) and QRS (SC) score in 285 patients. Figures are percentages*

	EF<40%	*SC≥6*	*EF<40% and SC≥6*
Sensitivity	73	64	54
Specificity	73	56	78
Predictive value of a positive test	18	11	17
Predictive value of a negative test	97	95	95
Efficiency	73	56	76
High risk group	31	46	24

Since it has been suggested that the QRS score is more accurate for subgroups of patients[5 9] we separately examined patients with a first transmural anterior and inferior infarction (Figs. 2 and 3). Since these results are based on a much larger number of patients than reported by previous authors, they confirm that the QRS score is unable accurately to predict the ejection fraction in individual patients.

Since the electrocardiogram is a standard method that is universally available and inexpensive it still seemed worthwhile to assess its predictive value for late mortality after hospital discharge even if we found that the QRS score correlated rather weakly with ejection fraction. Hindman *et al*[6] recently delineated high and low risk groups of patients after myocardial infarction by the use of Wagner's QRS score. As expected, in our series patients who died had a higher QRS score than survivors (7·0(4·1) *vs* 5·4(3·7), p=0·05) and ejection fraction was lower (35(16)% *vs* 48(14)%, p<0·0001), suggesting more extensive myocardial damage. The accuracy of the QRS score to predict mortality was, however, lower than that of the ejection fraction (Fig. 3, Table 3). The most advan-

Table 2 *Late survival in 285 patients in whom the QRS score (SC) and radionuclide ejection fraction (EF) was measured. Figures are numbers of patients*

	QRS score		*Ejection fraction*		*EF<40% and SC≥6*
	≥6	*<6*	*<40%*	*≥40%*	
Non-survivors	14	8	16	6	12
Survivors	116	147	72	191	57
Total	130	155	88	197	69
Mortality	11	5	18	3	17

Table 4 *Correlation of left ventricular ejection fraction and Wagner's QRS score*

	No of patients	*Correlation coefficient*	*SEE (%)*	*Regression equation*
Present study	285	−0·60	12	EF=60−2·3×QRS score
Palmeri *et al*[5]	55	−0·88	6	EF=59−3·0×QRS score
Young *et al*[9]	172	−0·60	?	EF=59−2·3×QRS score
Seino *et al*[8]	32	−0·72	?	EF=59−2·1×QRS score
de Pace *et al*[7]	41	−0·61	?	EF=59−2·0×QRS score
Roubin *et al*[10]	181	−0·81	12	EF=66−3·3×QRS score

SEE, standard error of the estimate.

tageous cutoff points for the two individual tests were 40% for ejection fraction and 6 for the QRS score.

Identification of patients at high and low risk was thus possible with both the QRS score and the ejection fraction. Although the predictive value of a positive test (ejection fraction <40% or QRS score ≥6) was rather low for both tests, it was slightly better for ejection fraction: 18% of patients with an ejection fraction <40% died as did 11% with a QRS score ≥6. Such a low predictive accuracy for late death is not surprising because of the low incidence of mortality (7% in the present series). This means that only a very sensitive test is a good predictor of mortality, whereas the prediction of survival should be easier. In fact low risk patients could be identified by both methods with high accuracy (Table 3) since 97% of patients with ejection fraction >40% and 95% of those with a QRS score <6 were late survivors. Nevertheless, the efficiency of radionuclide ejection fraction remained superior to that of the QRS score (73% *vs* 56%). The combination of the worst outcome of the two tests (ejection fraction <40% and QRS score ≥6) did not provide a better prediction of mortality (Tables 2 and 3). In fact, even if the high risk group was slightly smaller compared with that defined by ejection fraction alone (24% *vs* 31%) the sensitivity was much lower (54% *vs* 73%).

We thank A Beelan, T Baardman, H Wolf, and H J ten Katen, who assisted in the establishment of the data bank used in this study, K van Duyvendijk, who performed most of the nuclear studies, and N B Hindman, Duke University, Durham, USA, who computed the QRS score of a random sample of our patients.

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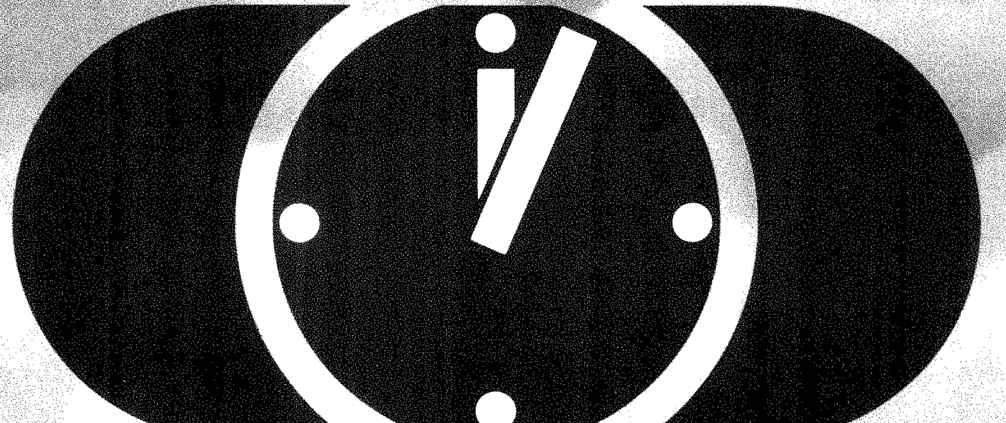

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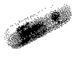
Angina, anxiety, essential tremor, thyrotoxicosis, prophylaxis of migraine.			
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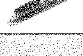
Hypertension where extra control is required.			

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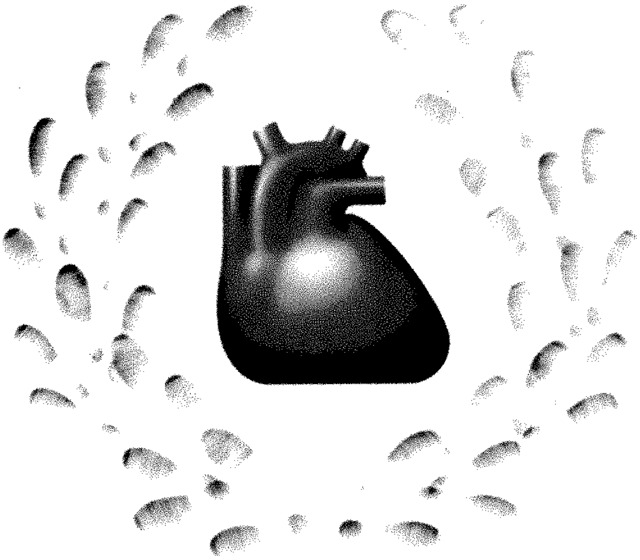

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Coronary thrombolysis with intravenous anisoylated plasminogen-streptokinase complex BRL 26921

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SUMMARY BRL 26921 is a protected plasminogen-streptokinase complex with selective affinity for thrombus. When given intravenously within three hours of the onset of a first acute myocardial infarction angiographic patency of the infarct related vessel was seen in all 16 patients receiving the active drug compared with only two of 16 receiving a placebo. There was relative sparing of left ventricular function in the active treatment group with anterior infarction (mean left ventricular ejection fraction 37% compared with 23% for placebo), but no significant difference in left ventricular function between the active and placebo groups was seen in patients with inferior infarction.

Intravenous BRL 26921 is highly effective in causing coronary reperfusion and may help to preserve left ventricular function when given early in the course of anterior infarction.

Myocardial infarction is associated with thrombotic occlusion of a coronary artery in a high proportion of patients during the first few hours of its onset.[1] Clinical studies have shown that reperfusion of previously occluded arteries is possible with thrombolytic agents and have suggested that infarct size may thus be limited.[2 3] Early reperfusion is important as myocardial salvage decreases rapidly, though variably, with time.[4]

Thrombolytic agents may be given intravenously or by direct intracoronary infusion. Earlier studies with intravenous streptokinase were difficult to interpret because reperfusion was not assessed angiographically and because many studies allowed entry up to 12 or even 24 hours after infarction. More recent studies with angiographic verification of reperfusion and more restricted entry criteria have shown reperfusion rates of between 60% and 80%.[5 6] Intravenous streptokinase infusion invariably causes systemic fibrinogenolysis and may produce a severe, albeit transient, haemorrhagic diathesis. Intracoronary administration of streptokinase is effective in producing thrombolysis but requires facilities for urgent cardiac catheterisation, which may well limit its applicability outside major cardiac centres. Moreover, despite the lower doses of streptokinase used systemic fibrinogenolysis remains a problem.

These disadvantages have led to a search for alternative thrombolytic agents[7] and to the development of BRL 26921,[8] a complex of streptokinase with anisoylated human plasminogen. The plasminogen selectively binds to fibrin rather than fibrinogen and causes the complex to seek out and bind to thrombus. Plasminogen is normally a potent activator of streptokinase, but to prevent premature activation while the complex is circulating it is temporarily inactivated by coupling an anisoyl group to its active site. This anisoyl group is removed by hydrolysis under in vivo conditions with a half life of approximately 37 minutes. After its removal, the streptokinase is activated and fibrinolysis occurs. In a previous study we showed that BRL 26921 was effective when given by the intracoronary route[9]; in theory it should be equally effective if given intravenously.

The present study was designed to assess the efficacy and safety of intravenous BRL 26921 in causing coronary reperfusion and myocardial salvage when given within three hours of the onset of myocardial infarction.

Patients and methods

The study protocol was approved by the local ethical committee. Patients were considered for entry into the study if they gave a history typical of acute

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myocardial infarction, with chest pain of longer than 30 minutes' but less than three hours' duration, had ST elevation of 2 mm or more in at least two electrocardiographic leads, and were able to give informed consent.

Exclusion criteria were age >70 years, systolic blood pressure <90 mm Hg or >200 mm Hg at the time of dosing, previous cerebrovascular accident, active peptic ulcer within one year, any surgery within one month, menstruation, previous treatment with streptokinase, and previous transmural myocardial infarction.

STUDY DESIGN

The primary object of the trial was to determine whether intravenous BRL 26921 was more likely than placebo to produce patent coronary vessels on angiography 90 minutes after drug administration. Although early coronary angiography performed on patients taking a placebo is in our experience both safe and helpful in subsequent management, we felt obliged to answer this question using the smallest practicable number of patients. For this reason the study was designed as a paired sequential analysis trial.[10] This is a well established technique for deciding whether an experimental treatment (BRL 26921) is significantly better than standard treatment using the minimum number of subjects. It involves trying each treatment alternately and scoring each pair of subjects as favourable to the experimental treatment, to standard treatment, or to neither. Pairs favourable to one or other treatment are plotted against the total number of pairs favourable (null pairs are ignored). The trial ends when the plot crosses one or other of two limit lines calculated from predetermined parameters. In the present study the parameters were set at $\alpha=0{\cdot}025$, $\beta=0{\cdot}2$, $u=3$, corresponding to a two tailed significance level of 0·05, a power of 80%, and an odds ratio of 3 or more in favour of the better process.

Randomisation was carried out independently at the two trial centres. The first step was to classify each patient as having an anterior infarct (ST elevation in leads V2, V3, or V4) or a non-anterior (inferior or lateral) infarct. Randomisation was carried out separately in these two groups to ensure equal numbers of active and placebo treatments. Treatment allocation was made using consecutively numbered vials of identical appearance containing either BRL 26921 (30 mg) or placebo (human serum albumin). Separate sets of vials were used for anterior and non-anterior infarct groups. There is a risk with this trial design of selection bias by guessing the next treatment allocation. We attempted to minimise this by randomising the order of active and placebo treatments within pairs and by leaving the decision to admit a patient to the study to an investigator who did not know the number of the vial to be used. We also checked retrospectively for comparability in patients allocated to active and placebo treatments and arranged for the double blind assessment of angiograms as described below.

As soon as possible after admission, a 19 gauge Venflon cannula was placed in a large peripheral vein for blood sampling and drug administration. Baseline samples of blood for measurements of coagulation factors, electrolyte concentration, and enzyme activities, and for blood grouping were taken. BRL 26921 or placebo was freshly reconstituted from freeze dried powder and given as a single intravenous injection. The initial 5 mg was given over five minutes and the remaining 25 mg over a further 10 minutes. Facilities for dealing with allergic reactions were available but were not in fact used. Blood was drawn for a repeat coagulation test one hour after dosing.

Coronary arteriography

Ninety minutes after the start of the BRL 26921 or placebo infusion coronary arteriography was performed in all patients using a procedure room within the coronary care unit, a portable image intensifier, and a videotape recorder. A 7 French gauge sheath was inserted percutaneously in the right femoral artery and arteriography was done by the Judkins's technique using non-ionic contrast medium (Niopam). Heparin was not used. For inferior infarcts the right coronary artery was injected first followed by the left coronary artery. For anterior infarcts the left coronary artery was injected first, followed in most patients by the right. At least two projections of each coronary artery were recorded. Results were classified as occlusions or reperfusions by a single observer who did not know which substance had been given and was not aware of the results of the coagulation test. As an additional safeguard, angiograms were reviewed retrospectively and in random order by an observer blind to patient identity to avoid the possibility of assessment bias from guessing the treatment given. The criterion for occlusion was an abruptly terminating stump of a major coronary vessel. The criterion for reperfusion was complete filling with contrast of the major coronary vessel in the infarct area within three cardiac cycles; almost invariably there was a severe proximal stenosis.

A prospective decision was made to give anticoagulants to all patients with reperfusion and withhold anticoagulants from all those with persistent coronary occlusion, irrespective of whether they had received BRL 26921 or placebo. The timing of introduction of heparin anticoagulation was based on the results of the one hour coagulation tests, repeated if necessary after four hours. Patients receiving anticoagulation treatment were given heparin by

Table 1 *Patient details, duration of symptoms, treatment received, and angiographic findings. For clarity patients are shown in pairs with placebo first.*

Case No	*Sex*	*Age (yr)*	*Time of onset to treatment (hr)*	*Treatment*	*Angiographic findings and reperfusion classification*
			Inferior infarct group		
1	F	68	2·5	P	Occluded RCA
2	M	56	2·5	A	Patent, stenosed RCA
3	M	36	2·75	P	Occluded RCA
4	M	64	3·0	A	Patent, stenosed RCA and Cx artery
5	M	50	3·0	P	Occluded Cx artery
6	F	66	2·75	A	Patent, stenosed RCA
7	M	57	3·0	P	Occluded RCA
8	F	65	2·0	A	Patent, stenosed RCA
9	M	60	1·25	P	Occluded RCA
10	M	46	2·25	A	Patent, stenosed RCA
11	M	62	3·0	P	Occluded RCA
12	M	43	1·5	A	Patent, stenosed RCA
13	M	39	2·0	P	Occluded Cx artery
14	F	61	3·0	A	Patent, mildly stenosed RCA
15	M	39	2·25	P	Occluded RCA
16	M	71	3·25	A	Patent, severely stenosed RCA
17	F	55	1·75	P	Occluded RCA
18	M	49	2·75	A	Patent, stenosed RCA and Cx artery
			Anterior infarct group		
19	M	58	3·0	P	Occluded LAD artery
20	M	51	2·25	A	Patent, LMS and three vessel disease
21	M	59	2·5	P	Occluded LAD artery
22	M	47	1·5	A	Patent, stenosed LAD artery
23	M	55	2·75	P	Occluded LAD artery
24	M	54	2·75	A	Patent, stenosed LAD artery
25	M	61	2·25	P	Occluded LAD artery
26	M	50	3·0	A	Patent, stenosed LAD artery
27	M	47	3·0	P	Occluded LAD artery
28	M	67	2·0	A	Patent, stenosed LAD artery
29	M	64	3·25	P	Patent, stenosed LAD artery
30	M	56	2·25	A	Patent, stenosed LAD, occluded RCA
31	M	47	2·75	P	Patent, stenosed Cx artery
32	M	43	1·50	A	Patent, stenosed LAD artery

A, active; P, placebo; RCA, right coronary artery; Cx, circumflex; LAD, left anterior descending; LMS, left main stem.

intravenous infusion pump at a rate sufficient to prolong the thrombin time by 50–100%. Heparin was given for five days and followed with oral warfarin anticoagulation. The sheath was removed within 24 hours.

Additional investigations

Coagulation indices—Previous experience with this drug indicated that measurements of coagulation indices one hour after dosing gave values close to those of maximum effect. Fibrinolysis and fibrinogenolysis were assessed by measurement of the euglobulin clot lysis time and plasma fibrinogen concentration. Prothrombin time ratio, thrombin time, partial thromboplastin time, packed cell volume, and platelet count were also measured. Additional information was given by the plasma clotting time with reptilase (the reptilase time),[11] which gives a direct measure of the anticoagulant effect of any fibrinogen degradation products on the coagulability of circulating fibrinogen.

Creatine kinase activity—Serial estimations were made of plasma creatine kinase activity at two hourly intervals for 24 hours.

Radionuclide ventriculography—Left ventricular function was assessed in all Edinburgh patients (n=22) by gated blood pool radionuclide ventriculography in the left anterior oblique projection between the eighth and tenth day after admission. The person conducting the test was unaware of the treatment given. Results were analysed separately for anterior and non-anterior infarct groups. Statistical comparison was by an appropriate non-parametric test (Mann Whitney U test).

Results

Table 1 shows patient details, treatment received, and angiographic findings. A total of 35 patients were seen who fulfilled the entry criteria and were offered participation in the trial. Three patients declined admission to the study and received standard treatment. Twenty two patients were studied in Edinburgh (10 with anterior and 12 with inferior infarcts) and 10 in Glasgow (four with anterior and six with inferior infarcts). There were equal numbers of patients receiving active treatment and placebo in each centre and in each group. All patients with anterior infarcts were male, and there were two female patients in both

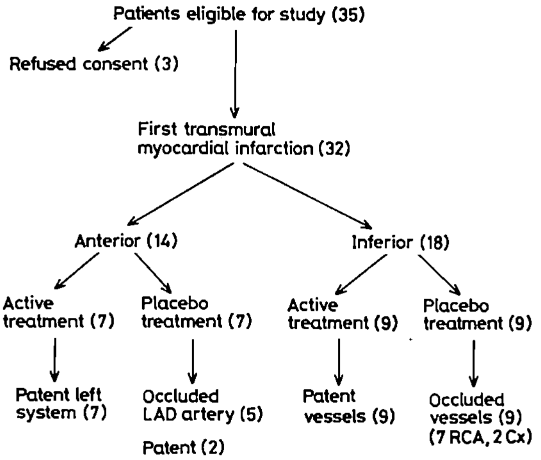

Fig. 1 *Flow chart showing composition of trial. LAD, left anterior descending; RCA, right coronary artery; Cx, circumflex (artery).*

treatment groups with inferior infarcts. The mean age for those receiving active treatment was 58 (10) years (inferior) and 54(8) years (anterior) compared with 52 (11) years (inferior) and 56 (7) years (anterior) for the placebo group. The duration of chest pain before treatment was 2·4 (0·6) hours and 2·6 (0·5) hours for active and placebo groups respectively. There was no significant difference between active and placebo groups in terms of pulse rate, blood pressure, or signs of cardiac failure on admission to the study.

Figures 1 and 2 summarise the results.

REPERFUSION

In all patients receiving active treatment the vessel expected to be the cause of the infarction was patent at angiography. All but one of these patients had patency of all three major coronary vessels. Most patients had a severe stenosis in the presumed infarct related vessel, although the degree of stenosis was variable. Additional disease was seen in 50% of the patients, and one had a left main stem stenosis.

In the inferior infarct group receiving placebo seven patients had total occlusion of the right coronary artery and two of the left circumflex coronary artery—that is, nine occluded vessels in nine patients. Five of seven patients in the anterior placebo group had total occlusion of a left anterior descending vessel. In the remaining two patients early spontaneous reperfusion may have occurred.

LEFT VENTRICULAR FUNCTION

Radionuclide ventriculography performed 8 to 10 days after admission showed a variable pattern in the inferior infarct group, with a tendency to better left ventricular function in the active treatment group which did not reach statistical significance (ejection fraction 44(5)% active, 40(8)% placebo) (Table 2). There was an appreciable difference in the anterior infarct group, with an ejection fraction of 37(7)% in those receiving active treatment compared with 23(5)% in the placebo group ($p<0\cdot05$, Table 2).

CARDIAC ENZYME ACTIVITY

All patients had a significant increase in plasma creatine kinase activity, signifying myocardial damage. The shape of the curve for serial measurements was appreciably different for the active and placebo groups, with a much earlier peak in the active group (Fig. 3).

COAGULATION INDICES

Changes in coagulation test results are shown in Table 3. The pretreatment coagulation test showed no major abnormality in any patient. The test results one hour after treatment showed no change in those who received placebo. Variable but significant changes in coagulation indices were seen in the active treatment group. Mean plasma fibrinogen concentrations fell from 3·1 to 1·2 g/dl. The mean reptilase time was prolonged from 19 to 51 s and the mean thrombin time from 11 to 38 s.

MORTALITY

There were two late deaths, both in the placebo group.

Case 5—A 50 year old man with an inferior infarct

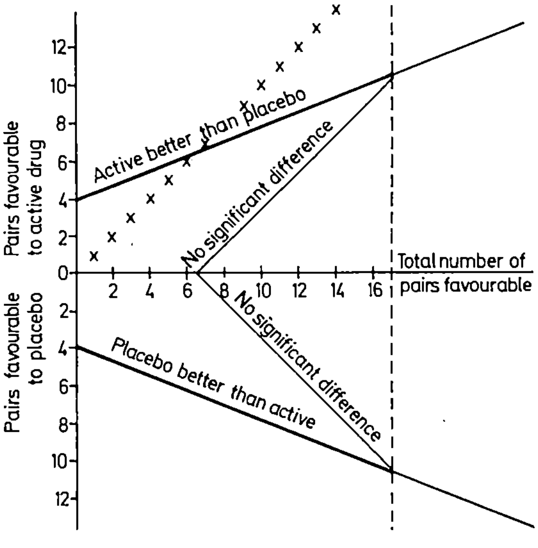

Fig. 2 *Sequential analysis with respect to reperfusion. α was taken as 0·025 and β as 0·2. X indicates favourable pairs.*

Table 2 *Individual and mean radionuclide left ventricular ejection fraction at 10 days in patients with anterior and inferior infarction receiving placebo or active treatment*

Case No	*Active group*	*Case No*	*Placebo group*
	Anterior infarction		
20	48	19	23
22	33	21	28
24	38	23	26
26	32	25	29
28	33	27	16
Mean (SD)	37 (7)	Mean (SD)	24 (5)
	Inferior infarction		
2	35	1	38
4	49	3	45
6	42	5	25
8	44	7	49
10	47	9	44
12	49	11	38
Mean (SD)	44 (5)	Mean (SD)	40 (8)

made good initial progress but subsequently developed left ventricular failure. Ejection fraction was 25%. Ten days after admission he collapsed with ventricular fibrillation and could not be resuscitated.

Case 2—A 59 year old man with an anterior infarct had a straightfoward clinical course; left ventricular ejection fraction was 23%. Three days after discharge (13 days after admission) he developed further chest pain. He did not seek immediate medical attention and died suddenly at home.

HAEMORRHAGIC COMPLICATIONS

There were two serious haemorrhagic complications and one minor complication. None was fatal.

Case 20—A man aged 51 with an anterior infarct received active treatment. Angiography showed all vessels to be patent, but there was three vessel coronary disease and left main stem stenosis. Treatment with heparin was started, and six hours later he vomited "coffee grounds" and became hypotensive. Heparin was withdrawn and blood transfusion restored his blood pressure. Endoscopy showed gastric erosions. Left ventricular ejection fraction was 48%, and repeat angiography confirmed patency of all vessels. Coronary bypass grafting was successfully performed 18 days after admission. Thirty years previously he had had a Polya gastrectomy for duodenal ulceration but had not subsequently complained of abdominal symptoms.

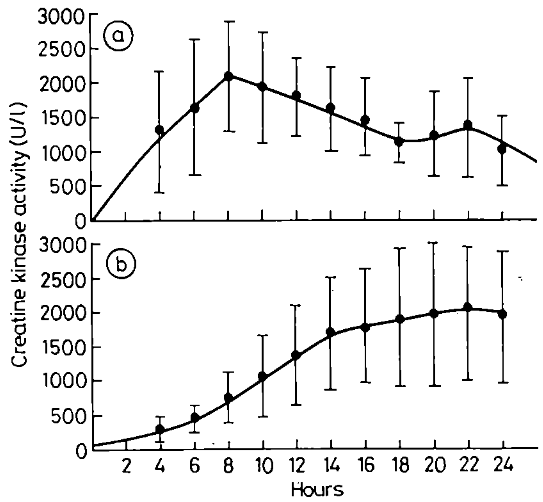

Fig. 3 *Two hourly creatine kinase measurements in patients given (a) active treatment and (b) placebo.*

Case 8—A 65 year old woman collapsed at a bus stop with chest pain. On admission the electrocardiogram showed an inferior infarct, and she was also noted to have a small scalp laceration. She received active treatment. During the night after admission she became drowsy, and an emergency tomogram showed an intracerebral haematoma. Heparin was withdrawn, and the haematoma was evacuated surgically 34 hours after admission. She made a slow but complete neurological recovery.

Case 2—A 56 year old man with an inferior infarct received active treatment. Two days after angiography he developed a haematoma at the site of the femoral puncture. Heparin was withdrawn, and an hour later he complained of chest pain and showed further electrocardiographic changes and a further rise in cardiac enzyme activity. There were no sequelae.

Table 3 *Coagulation indices before and one hour after administration of BRL 26921 (active) or placebo. Values are mean (SD)*

	Placebo		*Active*	
	Before	*After*	*Before*	*After*
Fibrinogen (g/dl)	2·8 (0·9)	3·1 (1·0)	3·1 (0·9)	1·2 (0·5)
Euglobulin lysis time (min)	>200	>270	>160	6 (7)
Prothrombin time ratio	1·0 (0·1)	1·0 (0·1)	1·1 (0·1)	1·8 (0·4)
Thrombin time*	1 (1)	1 (1)	1 (1)	27 (28)
Partial thromboplastin time*	−3 (3)	3 (2)	5 (8)	61 (71)
Reptilase time*	0·4 (0·7)	0·6 (1·0)	2·7 (2·5)	32 (29)
Platelet count ($\times 10^9$/l)	202 (53)	212 (39)	253 (55)	261 (58)
Packed cell volume (%)	45 (2)	46 (3)	45 (4)	45 (4)

*Prolongation from control value in seconds.

ARRHYTHMIAS

Arrhythmias within the first six hours of admission were more common in the active treatment group. In the placebo group sinus bradycardia with hypotension occurred in two patients (one requiring temporary atrial pacing), while frequent ventricular extrasystoles or short bursts of idioventricular rhythm occurred in a further three. In the active treatment group, one patient had an episode of ventricular fibrillation, two had idioventricular rhythm, one sinus bradycardia with hypotension, one atrioventricular dissociation, and one right bundle branch block. In addition, self terminating ventricular tachycardia occurred in three patients several hours after angiographically confirmed reperfusion.

Discussion

This study shows that BRL 26921 in a dose of 30 mg is effective in causing reperfusion of occluded coronary arteries within 90 minutes of its administration. The finding of total coronary occlusion in all but two of the placebo group contrasts with that of coronary patency in all those receiving the active drug. The probability of this result arising by chance is very small (the confidence limit of $p<0{\cdot}05$ from the sequential analysis chart is conservative; χ^2 with Yates's correction = 21·7, corresponding to $p<0{\cdot}001$).

BRL 26921 seems to cause less systemic defibrination than an equivalent dose of streptokinase.[12] Any thrombolytic agent may, however, cause haemorrhage if the patient already has damaged vessels sealed only by thrombus, and this could have accounted for the serious bleeding complications in two of our patients. There was no correlation in the present study between bleeding complications and the extent of defibrination. One problem affecting both streptokinase and BRL 26921 is inactivation by circulating antistreptococcal antibodies. Because of the varying concentrations of these antibodies in the general population there is no uniformly applicable dose-response curve. In order to achieve an adequate amount of thrombolytic activity in the majority of patients we used a fairly large dose of 30 mg BRL 26921, equivalent to 1·5 million units of streptokinase. This probably meant that some patients received a relative overdose, but there is as yet no rapid test for determining the titre of antistreptococcal antibodies to allow the individual dose to be tailored to the patient.

We believe that anticoagulation after reperfusion is important in maintaining patency of the reperfused vessel. Reinfarction in two of our patients was closely associated with cessation of anticoagulation, and we have seen a similar sequence in three other patients treated with BRL 26921 but not included in the present trial. The limited systemic lytic effect seen with this agent may actually be helpful in preventing reocclusion during the first few hours, but it may need to be supplemented with heparin.

The difference in effect on left ventricular ejection fraction between anterior and inferior infarction is not unexpected. Anterior infarction is well known to result in a greater reduction in left ventricular function than inferior infarction, and this accords with our finding of better preservation of left ventricular ejection fraction in the active anterior infarct group, while both active and placebo patients in the inferior infarct group had relatively well preserved ventricular function. Although our study group consisted only of patients with a first myocardial infarction the resting ejection fraction at 10 days was rather low in both active and placebo groups compared with the expected mean value of 36% based on the work of Dewhurst and Muir.[13] Our entry criteria may have tended to select patients with more pronounced early electrocardiographic changes, more severe symptoms leading to earlier arrival in hospital, and hence larger potential infarcts.

Although the pattern of creatine kinase release with coronary reperfusion is altered, with a large early peak and rapid decline, the total amount of enzyme released is still thought to correlate with infarct size.[14] In view of the altered shape of the curve in the group with reperfusion we did not feel confident about comparing the area under the curve for the two groups, as extrapolation on from 24 hours may be unreliable.

The numbers in this study are much too small to allow valid data on mortality. Patients who have survived for two or three hours after coronary occlusion are already to some extent "selected" for survival, and we further reduced expected mortality by excluding hypotensive patients. The association of prognosis with ejection fraction does, however, give cause for optimism.[13] As yet the best treatment after reperfusion is unclear, and this is likely to influence long term results.

We believe that BRL 26921 is a significant advance in thrombolytic treatment in myocardial infarction. It is potentially widely available and can be given as an intravenous bolus with a high probability that reperfusion will occur within a reasonable time scale. With close attention to exclusion criteria complications can be kept to a minimum.

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Emergency coronary artery bypass surgery after intracoronary thrombolysis for evolving myocardial infarction

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SUMMARY Sixteen patients underwent emergency coronary artery bypass surgery immediately after intracoronary streptokinase infusion for acute evolving myocardial infarction. Of these, 11 patients had 70% residual stenosis in the recanalised vessel, and in five thrombolysis was unsuccessful. There were no hospital deaths. All the patients sustained myocardial necrosis, the peak activity of creatine phosphokinase correlating with the time to reperfusion. Chest tube drainage (mean 960 ml) was significantly higher than for control patients but did not correlate with the total dosage of streptokinase. No patients had further myocardial infarction or developed recurrent angina.

Selected patients may benefit from coronary bypass surgery after intracoronary streptokinase infusion. If necessary this may be performed immediately with low mortality and morbidity.

The importance of left ventricular function in determining the prognosis of patients with coronary artery disease[1 2] has directed attempts towards early restoration of coronary blood flow in patients with acute evolving myocardial infarction. The infusion of streptokinase into the appropriate coronary ostium restored patency in 72–95% of patients.[3 4]

Nevertheless, though successful streptokinase treatment results in thrombolysis it does not remove the underlying coronary artery stenosis, and thus secondary occlusion with reinfarction remains a problem.[5 6] Serruys *et al* suggested a combination of transluminal angioplasty after successful thrombolysis,[3] while Phillips *et al* recommended coronary bypass surgery for stenoses not responding to streptokinase treatment.[7]

To obviate both these problems we adopted a policy of immediate coronary bypass surgery after intracoronary streptokinase infusion in selected patients.

Patients and methods

During 1983, 28 patients admitted to this hospital with acute evolving myocardial infarction[8] were treated by intracoronary streptokinase infusion. Thrombolysis was unsuccessful in five (18%) patients, including two with cardiogenic shock and one with intractable ventricular arrhythmias. Eleven (39%) patients had residual stenosis of >70% in the recanalised vessel and were considered at high risk of reocclusion. These 16 patients underwent immediate coronary bypass surgery, and they constitute the study group.

All 16 patients were male, with a mean age of 53 (range 38–60) years. All presented with unremitting angina associated with ST segment elevation on the electrocardiogram. None had developed Q waves. This was the first coronary occlusion in all patients. The mean interval between the onset of pain and coronary arteriography was 2·2 (range 1–4) hours. All patients had occlusion of one major coronary artery (anterior descending (12), right coronary artery (3), large first obtuse marginal (1)). In each case the left ventriculogram showed segmental wall motion abnormalities associated with the occluded vessel. An initial bolus of 20 000 units of streptokinase was infused into the occluded coronary artery followed by an infusion of 5000 units/min. The mean dose of streptokinase was 200 000 units (range 95 000–340 000 units). In two patients with cardiogenic shock streptokinase infusion was stopped after 15 minutes (equivalent to 95 000 units). A third patient developed intractable ventricular arrhythmias, and the streptokinase infusion was stopped after 100 000

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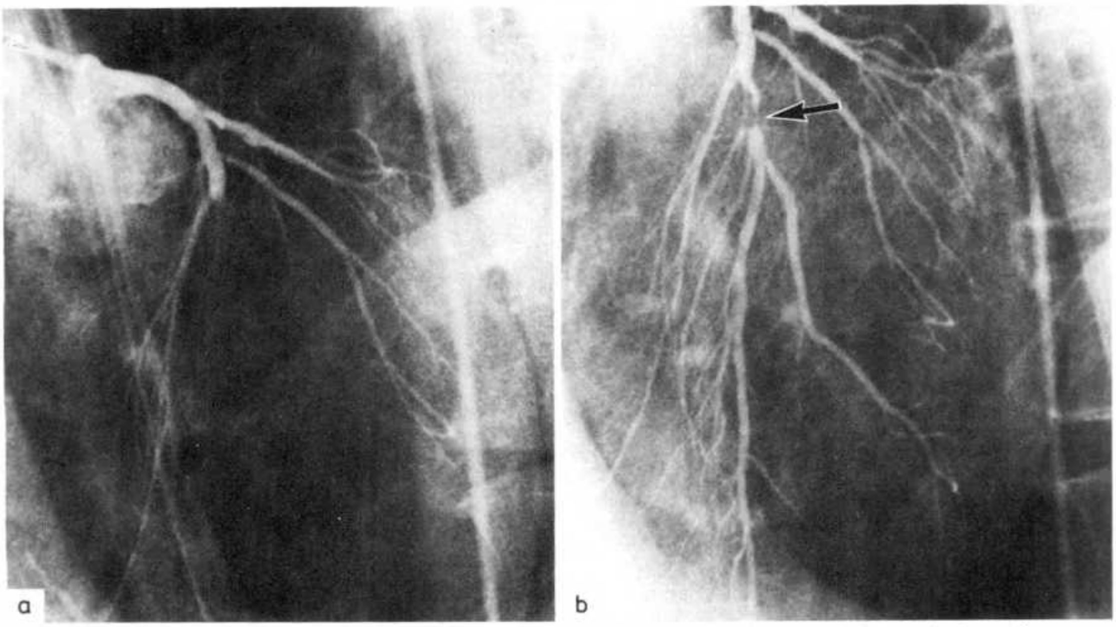

Fig. 1 *Coronary ateriograms (a) before and (b) after successful intracoronary thrombolysis of occluded anterior descending artery. (b) shows residual 90% stenosis (arrow).*

units had been given. All recanalised vessels had proximal stenoses of >70%, and in eight patients the stenosis was >90% (Fig. 1).

The patients were transferred immediately from the catheter laboratory to the operating room. Cardiopulmonary bypass was rapidly instituted between the right atrium and the ascending aorta. Coronary artery bypass surgery was performed using the technique of intermittent ischaemic arrest at moderate hypothermia (30°C). The occluded artery was grafted first so that the time between the onset of pain and complete reperfusion of the occluded artery was less than six hours in each case. All other major vessels with stenoses of >50% were then serially bypassed. Eight patients received three grafts, five patients two grafts, and three patients one graft. At the end of the operation the patients were given 10 units of cryoprecipitate, 10 units of platelets, and 2 units of fresh frozen plasma.

In the immediate postoperative period the development of myocardial necrosis was monitored by serial creatine phosphokinase measurements and electrocardiographic changes. Serum creatine phosphokinase activity was measured at eight, 16, and 24 hours after admission to hospital. Electrocardiograms were recorded on the first, second, third, and seventh postoperative day.

Results

There were no hospital deaths. Four patients required positive inotropic support (dobutamine 5–12 μg/kg/min) and one balloon counterpulsation. Six patients received a lignocaine infusion (2 mg/min) for ventricular arrhythmias. The mean blood loss through the chest tube drain was 960 (SD 385) ml. This was higher than for control patients but did not correlate with the total dose of streptokinase given

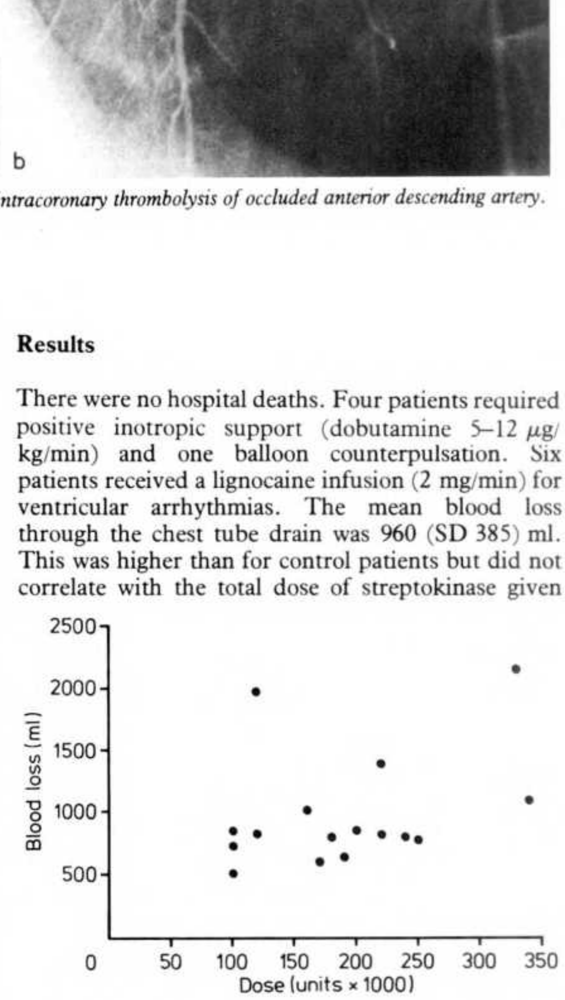

Fig. 2 *Relation between blood loss and streptokinase dose.*

Table *Indices of myocardial necrosis*

Case No	*Occluded vessel*	*No of grafts*	*Interval to reperfusion (hours)*	*New ECG changes*	*Peak CPK activity (IU/l)*
1	LAD	1	2	Normal	540
2	LAD	1	2	Normal	890
3	LAD	2	2	R	990
4	LAD	3	2	R	2500
5	RCA	1	3	Q	1800
6	LAD	2	3	R	1900
7	LAD	3	3	R	1950
8	LAD	2	3	R	2100
9	Lat Cx	2	3	Q	2500
10	LAD	3	3	Q	3500
11	RCA	2	4	Q	2800
12	LAD	3	4	R	3000
13	LAD	3	4	Q	3700
14	LAD	3	5	R	2000
15	LAD	3	6	R	2500
16	RCA	3	6	Q	5500

LAD, left anterior descending; Lat Cx, lateral circumflex; RCA, right coronary artery; ECG, electrocardiogram; R, loss of R wave progression across anterior chest leads; Q, new Q waves; CPK, creatine phosphokinase.

(r=0·36) (Fig. 2). One patient required re-exploration for excessive haemorrhage.

All patients had myocardial necrosis confirmed by serial electrocardiogram changes and enzyme studies. The Table summarises the data of individual patients. All four patients with occlusions of the right coronary artery or obtuse marginal vessels and two with occlusions of the anterior descending artery developed new Q waves. Eight patients with occlusions of the anterior descending artery showed a loss of R wave progression on serial electrocardiograms. In two patients (Table, cases 1 and 2) the electrocardiogram returned to normal. The postoperative value for creatine phosphokinase activity was abnormally raised (mean 2323 (SD 1561) units) with a positive MB isoenzyme in all patients. Three patients with occlusion of the anterior descending artery underwent successful thrombolysis within two hours of the onset of pain. The highest value for creatine phosphokinase activity in these patients was <1000 units (Table, cases 1–3). Figure 3 shows the correlation between the peak value for creatine phosphokinase activity and the time interval to reperfusion (r=0·67, p<0·01).

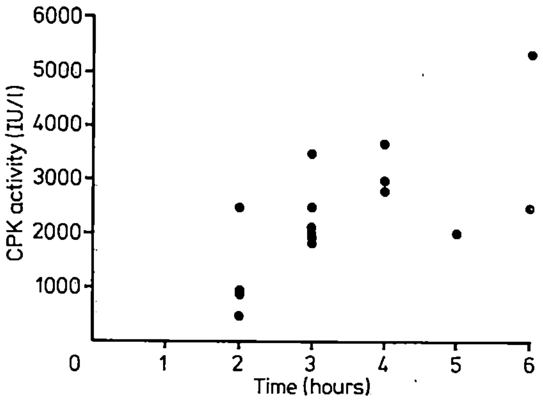

Fig. 3 *Relation between peak value of creatine phosphokinase (CPK) activity and time to reperfusion.*

Follow up in this series was short (mean 8 months). Nevertheless, to date no patients have experienced further angina or suffered myocardial infarction.

Discussion

An analysis of the results of the 63 coronary care units in Boston, Massachusetts, showed no perceptible fall in the hospital mortality from acute myocardial infarction between 1973–74 and 1978–79.[9] The most rational approach to the management of acute evolving myocardial infarction is the restoration of anterograde blood flow. After coronary artery occlusion in dogs, necrosis begins in the subendocardial region and spreads outwards to the subepicardial layer. This wavefront of necrosis can be arrested by reperfusion,[10] the final size of the infarction being a function of the duration of ischaemia and the ischaemic tolerance of a given patient. This in turn depends on the number and size of collateral vessels compensating for the occluded artery.

In 1960 Boucek and Murphy infused fibrinolysins into the aortic sinuses of patients with acute myocardial infarction, reporting circumstantial evidence that the manoeuvre resulted in the re-establishment of blood flow.[11] This technique was refined by Rentrop *et al* who reported the first successful cases of intracoronary thrombolysis in 1979.[12] The sooner the treatment is started, the greater its chance of success.[13 14] Successful streptokinase treatment has been associated with improved thallium-201 uptake[15–17] and improved wall motion[18–20] in the ischaemic areas. The clinical results of thrombolysis have also been encouraging.[6 18] In the German multicentre study mortality was 7% among patients in whom reperfusion occurred and 24% among those in whom the occlusion persisted.[6] After successful thrombolysis reocclusion has been reported in 17%[3] to 25%[5] of patients. Serruys *et al* suggested concomitant balloon dilatation of the residual stenosis after successful thrombolysis, reporting no late reocclusions in 18 patients undergoing this procedure.[3] Krebber *et al* have used thallium-201 scintigraphy as a predictor of the salvageability of myocardium immediately after intracoronary thrombolysis to assess patients suitable for early coronary revascularisation.[21] No details of the patients undergoing this procedure are given, however, nor is the time interval between medical recanalisation and surgical reperfusion stated.

Berg *et al* have been strong advocates of immediate coronary bypass surgery for acute evolving myocardial infarction.[8] DeWood *et al* reported appreciable improvement in global function and regional wall motion in selected patients if surgical reperfusion was performed within six hours of the onset of symptoms of anterior infarction.[22] Phillips *et al* used immediate coronary bypass surgery for 21 patients in whom streptokinase treatment failed.[7] The mean interval to reperfusion was 10 hours in this group, four of which required re-exploration for haemorrhage. Becher *et al*, however, found no increase in bleeding complications in patients operated on within 24 hours of thrombolysis compared with those undergoing surgery after this period.[23]

The results of our study support the aggressive approach in treating patients with acute evolving myocardial infarction.[7 8 22] Thrombolytic treatment had failed in five patients, two of whom were in cardiogenic shock, while in eight the residual stenosis after successful thrombolysis was >90%. The anatomy of the latter group of patients was more severe than that reported by Serruys *et al*, who found that only 19% of 64 patients undergoing thrombolysis had a residual stenosis of >70%.[3] In no case did the combination of rapid intracoronary thrombolysis followed by immediate coronary bypass surgery prevent myocardial damage. We consider, however, that it may have limited its extent. This was particularly apparent in two patients in whom blood flow was re-established within two hours of the onset of pain (Table, cases 1 and 2). In these patients peak creatine phosphokinase activity was <1000 IU/l and the electrocardiogram returned to normal. The follow up period was short, but to date there have been no deaths, mechanical complications of infarction, or further ischaemic episodes.

Theoretically, all patients having acute evolving myocardial infarction should be revascularised at the earliest possible opportunity. As a prelude all patients will undergo coronary arteriography to delineate the anatomy. Successful thrombolysis with intracoronary streptokinase then provides additional time before a decision regarding surgery must be taken. The length of time depends partly on the residual coronary lesions. Some may be so minor that the infarction can be allowed to run its course and elective surgery planned at a later date when further symptoms occur.[24] This more elective approach would allow the use of the internal mammary artery which must now be considered as the conduit of choice for the anterior descending artery.[25 26] In other situations a more aggressive approach may be required. This may take the form of immediate balloon angioplasty[3] or early surgery.

Since this was not a prospective randomised trial with follow up haemodynamic data, we are unable to conclude that this is the preferred method of treatment. The study simply shows that immediate coronary bypass surgery can be performed effectively after intracoronary thrombolysis. Though postoperative chest tube drainage was significantly higher in this group of patients than after elective coronary bypass surgery, haemorrhage was not an insuperable problem. Indeed in the dosage given (95 000–340 000 units) there was no correlation between the dosage and total blood loss. Though Jutzy *et al* have shown no difference in the systemic fibrinolytic state assessed by serial determinations of fibrinogen and euglobulin lysis time,[27] it is likely that the larger doses (>500 000 units) given intravenously[28 29] may preclude immediate surgery.

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Coronary artery disease and haemostatic variables in heterozygous familial hypercholesterolaemia

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SUMMARY Haemostatic variables were measured in 61 patients with heterozygous familial hypercholesterolaemia, 32 of whom had evidence of coronary heart disease. Age adjusted mean concentrations of plasma fibrinogen and factor VIII were significantly higher in these patients than in the 29 patients without coronary heart disease, but there were no significant differences in serum lipid concentrations between the two groups. Comparisons in 30 patients taking and not taking lipid lowering drugs showed lower values for low density lipoprotein cholesterol, high density lipoprotein cholesterol and antithrombin III, and a higher high density lipoprotein ratio while receiving treatment. The results suggest that hypercoagulability may play a role in the pathogenesis of coronary heart disease in patients with familial hypercholesterolaemia.

Premature coronary disease is a characteristic feature of heterozygous familial hypercholesterolaemia and up to 50% of male and 25% of female patients with familial hypercholesterolaemia develop symptoms of coronary ischaemia by the age of 50.[1 2] Increased concentrations of low density lipoprotein (LDL) play a major role in the pathogenesis of this premature atherosclerosis, but accelerated intravascular coagulation[3] and increased plasma fibrinogen concentrations have also been reported.[4 5] Preliminary results from the Northwick Park heart study have shown an association between high plasma concentrations of factor VII, factor VIII, and fibrinogen and an increased risk of subsequent cardiovascular death.[6] We have therefore measured these and other haemostatic variables in patients with familial hypercholesterolaemia with or without overt coronary heart disease and in addition have studied the effects of hypolipidaemic drugs on these variables.

Patients and methods

Sixty one patients (34 men, 27 women) aged 20–71 (mean 45) years with heterozygous familial hypercholesterolaemia were studied. Familial hypercholesterolaemia was defined as serum cholesterol concentration >7·5 mmol/l in an adult or >6·7 mmol/l in children under the age of 16, together with tendon xanthomata or with hypercholesterolaemia plus tendon xanthomata or hypercholesterolaemia plus premature coronary disease (before the age of 60) in a first degree relative. Tendon xanthomata were present in 57% of patients. Most patients had a type IIa phenotype, but seven had raised serum triglyceride concentrations (>2 mmol/l) and a type IIb phenotype. All patients were receiving a low cholesterol diet, four had had a partial ileal bypass, and 44 were taking hypolipidaemic drugs (cholestyramine 17, probucol 8, clofibrate 6, neomycin 1, cholestyramine and clofibrate 6, cholestyramine and neomycin 6). The presence of significant coronary disease was defined on the basis of one or more of the following: a reduction of ≥50% in the luminal diameter of any major coronary artery when seen in two projections at coronary arteriography which was performed where there was a clinical indication; the presence of angina or a positive 16 lead exercise precordial map[7]; and electrocardiographic evidence of previous myocardial infarction.[8]

Coronary arteriograms were reviewed by two observers and assigned a score designed to denote the severity of disease based on the following criteria: 1, significant strictures (>50% reduction in luminal

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diameter seen in two projections) affecting a single vessel; 2, left main stem disease; 3 complete occlusion of the right coronary, the left anterior descending, or the left circumflex arteries.

Blood was taken from an antecubital vein between 0900 and 1200 hours after an overnight fast. Blood for assay of clotting factors was centrifuged at room temperature and the plasma stored in liquid nitrogen for subsequent assay.[9] Fibrinogen and biological activity of factors II, VII, VIII, and X and antithrombin III were measured by methods described elsewhere.[9,10] Serum triglyceride concentrations were estimated enzymatically,[11] and total cholesterol by an automated Leibermann-Burchard method.[12] High density lipoprotein (HDL) cholesterol was measured by the heparin-manganese precipitation technique[13] and the HDL ratio was calculated as HDL/total −HDL cholesterol. LDL cholesterol was estimated as described by Friedewald *et al.*[14] In 28 patients measurements were repeated 5–10 weeks after hypolipidaemic drugs had been withdrawn (n=22) or after previously untreated patients had started drug treatment (n=6). Seventeen patients were taking cholestyramine (Questran) in a dose of 16 g daily, either alone or in combination with neomycin 2 g daily or clofibrate 2 g daily, seven were taking probucol 1 g daily, and four clofibrate 2 g daily.

In the analyses comparing patients with and without coronary disease by unpaired *t* tests, mean values were adjusted to age 50 years using coefficients derived from multiple regression analyses of each coagulation or biochemical variable on coronary disease (present or absent), sex, and age. Data on treatment effects were analysed by paired *t* tests.

Results

A total of 32 patients (17 men and 15 women) (mean age 50·8, range 28–71 years) were identified as having coronary heart disease. This diagnosis was made on the following grounds: electrocardiographic evidence of myocardial infarction (5); coronary arteriographic abnormalities without infarct (6); coronary arteriographic abnormalities and infarct (10); and angina or a positive exercise precordial map or both (11). Seven patients had had previous coronary artery bypass surgery. The 29 patients without coronary disease, of whom 17 were men and 12 women, were younger than those with coronary disease (mean age 38·4, range 20–59 years).

There were no significant differences in any lipid variables between the two groups but mean concentrations of fibrinogen and factor VIII were significantly higher in the patients with coronary disease than in those without (Table 1). To see whether either of these differences could be accounted for by associations between factor VIII or fibrinogen and lipids, values for cholesterol, triglycerides, and HDL were included in further regression analyses as explanatory variables. The results did not differ materially from those shown in Table 1.

Untreated patients and those in whom hypolipidaemic drugs had been temporarily withdrawn had significantly higher LDL and HDL cholesterol concentrations and a lower HDL ratio compared with the treated state. Antithrombin III was significantly higher in patients not receiving treatment (90% *vs* 82%, $p<0·02$), but none of the other haemostatic variables showed any significant difference (Table 2). Table 3 shows the effects of individual drug regimens. The small number of patients in each group precludes detailed statistical analysis, but the decrease in antithrombin III concentrations appeared to be greatest in patients taking probucol.

Coronary arteriograms were performed in 16 patients (13 men, three women, mean age 44 years). Angiographic scores ranged from 1 to 9. The correlation between angiographic score and factor VIII was −0·27 (p=0·33) and for fibrinogen −0·10 (p=0·73).

Discussion

Premature and angiographically severe coronary dis-

Table 1 *Age adjusted plasma lipid and lipoprotein concentrations and haemostatic variables in patients with familial hypercholesterolaemia with and without coronary heart disease (CHD). Values are mean (SD)*

	With CHD (n=32)	*Without CHD (n=29)*	*p value*
Fibrinogen (g/l)	3·28 (1·00)	2·84 (0·60)	0·04
Factor II (%)	107 (30)	117 (22)	0·18
Factor VII (%)	123 (48)	122 (39)	0·92
Factor VIII (%)	136 (70)	102 (34)	0·02
Factor X (%)	87 (25)	81 (16)	0·30
Antithrombin III (%)	82 (17)	86 (20)	0·37
Total cholesterol (mmol/l)	8·23 (1·88)	8·00 (1·41)	0·59
LDL cholesterol (mmol/l)	6·49 (1·81)	6·35 (1·55)	0·74
HDL cholesterol (mmol/l)	0·99 (0·32)	1·03 (0·38)	0·65
HDL ratio	0·156 (0·082)	0·166 (0·093)	0·66
Triglyceride (mmol/l)	1·59 (0·75)	1·49 (0·59)	0·62

Conversion: SI to traditional units—cholesterol: 1 mmol/l≈38·6 mg/dl; triglyceride: 1 mmol/l≈88·5 mg/dl.

Table 2 *Effect of treatment on lipid concentrations and haemostatic variables in 30 patients with familial hypercholesterolaemia. Figures are mean values*

	With treatment	*Without treatment*	*SD of difference*	*p value*
Fibrinogen (g/l)	3·05	3·10	0·69	0·65
Factor II (%)	111	120	30	0·12
Factor VII (%)	119	115	27	0·44
Factor VIII (%)	122	124	35	0·75
Factor X (%)	83	88	21	0·25
Antithrombin III (%)	82	90	19	0·02
LDL cholesterol (mmol/l)	6·45	7·89	1·04	0·0001
HDL cholesterol (mmol/l)	0·98	1·06	0·18	0·02
HDL ratio	0·151	0·129	0·052	0·03
Triglyceride (mmol/l)	1·79	1·79	0·36	0·92

SD, standard deviation.
Conversion: SI to traditional units—cholesterol: 1 mmol/l≈38·6 mg/dl; triglyceride: 1 mmol/l≈88·5 mg/dl.

Table 3 *Mean changes (SD) in lipid concentrations and haemostatic variables in 28 patients with familial hypercholesterolaemia taking various drugs*

	Cholestyramine (n=10)*	*Cholestyramine and neomycin (n=4)*	*Cholestyramine and clofibrate (n=3)*	*Clofibrate (n=4)*	*Probucol (n=7)*
Fibrinogen (g/l)	+0·19 (0·79)	−0·44 (0·92)	−0·07 (0·32)	−0·01 (0·59)	−0·10 (0·69)
Factor II (%)	−18 (42)	−20 (34)	+11 (13)	+9 (7)	−9 (14)
Factor VII (%)	+2 (40)	−6 (20)	+22 (22)	+10 (13)	+4 (18)
Factor VIII (%)	−15 (29)	+13 (30)	+35 (48)	−5 (24)	−4 (41)
Factor X (%)	+2 (30)	−20 (24)	+4 (8)	−10 (13)	+2 (13)
Antithrombin III (%)	−7 (22)	−9 (14)	+3 (13)	−4 (13)	−12 (13)
LDL cholesterol (mmol/l)	−1·47 (1·51)	−3·37 (2·32)	−1·70 (0·24)	−1·16 (1·06)	−0·51 (1·02)
HDL cholesterol (mmol/l)	+0·01 (0·13)	−0·14 (0·13)	0·00	−0·14 (0·21)	−0·04 (0·29)
HDL ratio	+0·05	+0·04	+0·04	−0·02	0·00
Triglyceride (mmol/l)	−0·71 (2·47)	+0·08 (0·79)	−0·07 (0·12)	+1·85 (2·86)	−0·01 (0·80)

*Questran.
Conversion: SI to traditional units—cholesterol: 1 mmol/l≈38·6 mg/dl; triglyceride: 1 mmol/l≈88·5 mg/dl.

ease is common in heterozygous familial hypercholesterolaemia.[1 2 15] This premature disease is not solely a function of LDL concentrations; additional risk factors include a decrease in HDL cholesterol and in the HDL:LDL ratio,[16 17] smoking,[18] and a family history of premature death.[19] In addition, abnormalities in haemostatic function have been found both in familial hypercholesterolaemia and in men who later died of coronary heart disease. Thus the Northwick Park heart study found that plasma concentrations of factor VII, VIII, and fibrinogen as well as serum cholesterol concentrations were significantly higher at entry to the study in the 27 men who died of cardiovascular disease (mostly coronary heart disease) than in the 1461 survivors.[6] Lowe *et al* found significantly raised fibrinogen concentrations in patients with familial hypercholesterolaemia,[5] whereas Carvalho and Lees found evidence for activation of the intrinsic coagulation system (low prekallikrein and kallikrein inhibitor values and increased concentrations of soluble fibrin complexes).[3] Lowe *et al* also examined the relation between plasma fibrinogen concentrations, platelet aggregates, and coronary disease in familial hypercholesterolaemia.[5] They showed increased fibrinogen concentrations and increased numbers of platelet aggregates from the age of 15 onwards, which they suggested might be markers of the underlying atherosclerosis to which these patients are so susceptible. They failed to show any correlation between the serum cholesterol concentrations and the coagulation abnormalities, which were as evident in patients taking effective cholesterol lowering drugs as in untreated individuals.

Hypercoagulability could well play a role in the development of coronary disease since thrombotic coronary occlusion occurs in the majority of patients in the early stages of myocardial infarction.[20] High fibrinogen concentrations increase blood viscosity,[21] and increased viscosity may in turn impair blood flow,[22] thus predisposing to thrombosis. Small deposits of fibrin have been found on or just beneath the endothelium even in neonates[23] with a rapid increase in prevalence with increasing age. Smith and Staples found high concentrations of fibrinogen in atherosclerotic lesions from human aortic intima along with variable concentrations of factor VIII.[24] It remains debatable whether such abnormalities of haemostatic function play an initiating role in the pathogenesis of coronary disease or whether, as has been suggested,[6] they are simply markers of premature vascular disease and represent responses to arterial injury.

Previous studies have shown that lipid lowering diets and clofibrate tend to exert what would be expected to be a beneficial effect on haemostatic variables in patients with hypertriglyceridaemia.[25–27] Nevertheless, the slight but significant decrease in the thrombin inhibitor antithrombin III observed in our patients with familial hypercholesterolaemia while taking lipid lowering drugs is potentially adverse; this effect was most pronounced in patients taking probucol or cholestyramine in combination with neomycin, in whom a theoretically undesirable decrease in HDL cholesterol was also observed. Probucol and neomycin are each known to reduce both LDL and HDL,[28 29] but the decrease in HDL cholesterol was not seen in patients taking cholestyramine alone. The major effect of lipid lowering treatment overall was to decrease LDL cholesterol by 18%, which resulted in a significant increase in the HDL ratio. Comparable changes in a similar group of patients with hypercholesterolaemia treated with diet and cholestyramine for five years were recently shown to be associated with a reduction in the rate of progression of their coronary disease on angiography.[30 31]

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Reoperation for angina after previous aortocoronary bypass surgery

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SUMMARY A retrospective study was carried out of the outcome of 102 patients who underwent a second operation for myocardial revascularisation, necessitated by persistence or recurrence of intractable angina after their first coronary bypass procedures. Operative mortality was 2%. During follow up of the survivors (mean interval 36·4 months) five died, two after further operation, and five underwent further surgery. Sixty eight patients reported an improvement in their symptoms, 57 of whom claimed to have little or no angina. Less favourable results were recorded for those patients reviewed with longer follow up. No useful indicators of prognosis were identified.

The problem of angina in patients who have already received bypass grafts is likely to increase as more revascularisation surgery is performed. Reoperation offers a reasonable prospect of helping some of these patients, but not all will be suitable. Their long term prognosis remains uncertain.

Bypass graft surgery ameliorates or abolishes angina in the majority of patients who undergo operation,[1] but in some cases symptoms persist or recur. Angina may recur in 3·5–4·4% of patients each year.[2] Thus as more patients have undergone bypass surgery, and as the time elapsing after operation increases, the problem of angina in patients who have already undergone one myocardial revascularisation procedure will increase. Reoperation can be performed with a low risk and can improve or relieve angina in many patients, but the late results are less favourable than after the first attempt at revascularisation.[3]

The results of reoperations at the London Chest Hospital were reported in 1979.[4] We now report our further experience with a larger series of patients and the results of extended follow up of those who underwent operation initially. We sought to identify factors, which can be determined preoperatively, that may give an indication of the prognosis after reoperation.

Patients and methods

One hundred and two patients who underwent a second coronary bypass operation between 1972 and January 1982 were included in the study. Patients who had concurrent valve surgery were not included. The mean age of the patients was 52·7 (range 34–73) years. Nine patients were female. Nine were known to have diabetes mellitus and 19 hypertension, and 33 smoked >10 cigarettes a day at the time of reoperation. Serum cholesterol concentration was estimated in 58 patients and was found to be increased (>7·0 mmol/l (>300 mg/100 ml)) in 29.

FIRST OPERATION

At the first operation a mean of 2·1 grafts were placed per patient. Twenty seven patients received one graft, 39 two, 33 three, and three four. In addition 24 patients had endarterectomy performed to 33 vessels. Left ventricular aneurysmectomy was carried out in two patients. Twelve patients were considered to have had perioperative myocardial infarction as assessed by electrocardiographic criteria (development of pathological Q waves in nine or of bundle branch block in three). Table 1 gives details of the sites of graft placement.

RECURRENT ANGINA

The clinical indication for considering reoperation in all patients was severe angina either at rest or on minimal exertion which had proved refractory to medical management. All patients were investigated by selective coronary and graft angiography in three planes

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Table 1 *Sites of graft placement at first operations and reoperation. Figures indicate number of patients*

Graft site	*First operation*	*Reoperation*	
		New grafts	*Regrafts*
Left anterior descending artery (LAD)	76	13	44
Diagonal of LAD	14	2	7
Lateral circumflex branches	45 (3*)	43	21
Trifurcation branch	4	1	1
Right coronary artery before crux (RCA)	45	14	25
Posterior descending artery (PDA)	11	10	16†

*Patients who had grafts to two lateral circumflex branches.
†Includes patients in whom a RCA graft was placed before the crux at first operation and to the PDA at reoperation.

and left ventricular angiography in the right anterior oblique plane. Only those patients in whom it was technically feasible to place further grafts, and who therefore underwent surgery, are reported in this study.

The putative cause for the recurrence of angina was determined from the angiogram. Where a graft was occluded or significantly stenosed, or distortion at its insertion into the coronary artery was equivalent to such a stenosis, the graft was deemed to have failed. Progressive disease describes the development of a stenosis of >50% that was not apparent on the angiogram before the first operation. Revascularisation was considered to have been incomplete at the first operation if a vessel was not bypassed when it contained a stenosis of >50%. The terms progressive disease and incomplete revascularisation were applied only to vessels whose lumen diameter was >1 mm on the basis that the smaller vessels would be unsuitable to receive a vein graft.[5 6] The cause of recurrent angina was then categorised as (*a*) graft failure, (*b*) progressive disease, (*c*) incomplete revascularisation, or (*d*) various combinations of these factors.

REOPERATION

All the reoperations reported in this series were performed at the London Chest Hospital by one of three surgeons. The mean interval between the first and second operation was 37·1 (SD±28·6) months.

FOLLOW UP

The progress of patients during follow up after reoperation was assessed as far as possible from clinic attendances. For patients unable to attend the hospital information was obtained from questionnaires sent to the patients themselves, from their attending physicians, and from their general practitioners. Inquiry was made about the presence and severity of angina, which was graded as: 0, no angina; 1, angina occurring only on severe exertion; 2, angina occurring on moderate exertion; 3, angina occurring on minor degress of exertion; and 4, angina at rest. Symptoms and signs of left ventricular failure were sought. The medication taken by the patients was recorded.

In 47 patients maximal symptom limited progressive increment exercise testing was performed either by treadmill (modified Bruce protocol) or by bicycle ergometer. The reason for termination of the test, the maximum workload achieved, and the electrocardiographic changes were noted. Of these patients, 24 had previously performed an exercise test before reoperation so that a comparison between results was possible. The end point for follow up was the latest available clinical information—unless a further surgical procedure for revascularisation had been performed, when this was taken as the end point—or death. For the purposes of stratifying the patients into groups according to the length of follow up, the duration of follow up was taken from the time of reoperation until December 1982 for those patients who underwent further reoperation or who had died. Inquiry was made to the Registrar General at this date to ascertain if any patient had died, so that we consider that the survival data are complete.

Results

CAUSE OF RECURRENT ANGINA AFTER FIRST OPERATION

Table 2 shows the angiographic features thought to indicate the reason for recurrent angina and the time of this recurrence in the different groups. Overall, graft failure was considered to have occurred in 84 patients, progressive disease in 42, and revascularisation to have been incomplete in 34. Of the 27 patients who received a single graft at the first operation, revascularisation was considered incomplete in 10. For the remaining 17 patients a single graft was the appropriate procedure, and in only two of these was failure of this graft the sole cause of recurrent angina.

REOPERATION

At reoperation the mean number of grafts placed per patient was 1·97. Table 1 shows the distribution of

Table 2 *Putative cause(s) of recurrent angina after first operation and mean (SD) time until recurrent angina in each group*

Cause(s) of recurrent angina	*No of patients*	*Time of recurrence after first operaion (mnth)*
Graft failure only	31	11·1 (17·6)
Progressive disease only	12	20·9 (17·3)
Incomplete revascularisation only	3	4·3 —
Graft failure and incomplete revascularisation	24	18·1 (25·9)
Graft failure and progressive disease	23	30·7 (21·1)
Incomplete revascularisation and progressive disease	1	
Incomplete revascularisation, progressive disease, and graft failure	6	27·7 —
Not determined	2	

these grafts. Twenty nine patients received one graft, 49 two grafts, 23 three grafts, and one four grafts. Endarterectomy was performed on 24 vessels in 18 patients, four of whom had already had vessels endarterectomised at their first operation.

Twenty two patients received grafts only to vessels that had not been grafted at the first operation, 33 received grafts only to vessels that had previously received grafts, and the remaining 47 patients had a combined procedure. The term "vessel" refers to all coronary branches of sufficient size to accept a vein graft. In this context, for example, the diagonal branch of the left anterior descending artery if large enough to graft, would be considered a separate vessel to the main left anterior descending artery.

There were two operative deaths, and eight patients had perioperative myocardial infarction (new Q waves in six, bundle branch block in two). Table 3 lists the recorded complications. Of particular note, two patients suffered division of a previously placed graft to the left anterior descending artery during resternotomy. One of these patients developed an anterior myocardial infarction and later died of left ventricular failure, and the other died in the immediate postoperative period.

FOLLOW UP

Information was available on all 100 survivors at a mean interval of 36·4 (range 2–86) months. During follow up three patients died at three, 38, and 40 months without further surgery. Five patients proceeded to a third operation for myocardial revascularisation, and one underwent dilatation of his grafts during cardiopulmonary bypass. Two of these patients undergoing further surgery also subsequently died, and in one the cause of death was attributed to leukaemia. One other patient received a cardiac transplant. Sixty eight patients thought that their symptoms were improved, 14 that their condition was unchanged, and the remaining 13 survivors that their symptoms had become worse.

Table 3 *Numbers of patients in whom recorded operative complications occurred*

Death (within 24 hours)	2
Myocardial infarction	8
Resternotomy for bleeding	3
Other significant bleeding problems	2
Slow wound healing/dehiscence	3
Division of LAD graft at sternotomy (one died, included above)	2
Transient atrial fibrillation or flutter	6
Others*	6

*One instance each of renal failure, pulmonary embolism, haematuria with anticoagulants, ventricular fibrillation, thigh abscess, tear in superior vena cava.
LAD, left anterior descending artery.

For the following analyses the patients were divided into three groups according to their outcome:

Good result—This group comprised patients who had no angina or angina only on severe exertion (grades 0 and 1).

Intermediate result—This group comprised patients with angina on moderate exertion (grade 2).

Poor result—This group comprised patients who died, required a further operative procedure, developed severe left ventricular failure, or had angina on minimal exertion or at rest (grades 3 and 4). On the basis of these criteria 57 patients derived great benefit from their reoperation, 14 fell into the intermediate group, and 31 fared badly.

The type of operative procedure did not influence outcome. Good results were obtained in 52% of patients who had vessels regrafted only, in 59% of those who received only new grafts, and in 57% of those undergoing a combined procedure (Fig. 1). Results for outcome were less favourable for patients whose duration of follow up was 24 months or more compared with those who were reviewed earlier (Fig. 2). Tables 4 and 5 show the influence on outcome of a number of factors either determined before reoperation or which were a feature of the operations. The assessment of completeness of revascularisation at reoperation took account of vessels that were considered large enough to graft (>1·0 mm) (Table 5). Neither the cause of recurrent angina after the first operation nor the interval to that recurrence influenced outcome significantly. There was, however, a trend for this interval to be shorter in those patients whose outcome was unsatisfactory. When patients in whom incomplete revascularisation at the first operation was considered a contributory factor

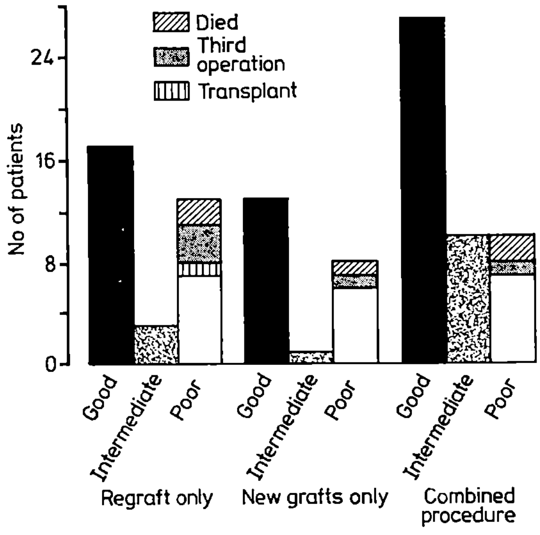

Fig. 1 *Outcome according to the type of operative procedure. Regraft only: patients in whom grafts were placed only in previously grafted vessels; new grafts only: patients in whom grafts were placed only into ungrafted vessels.*

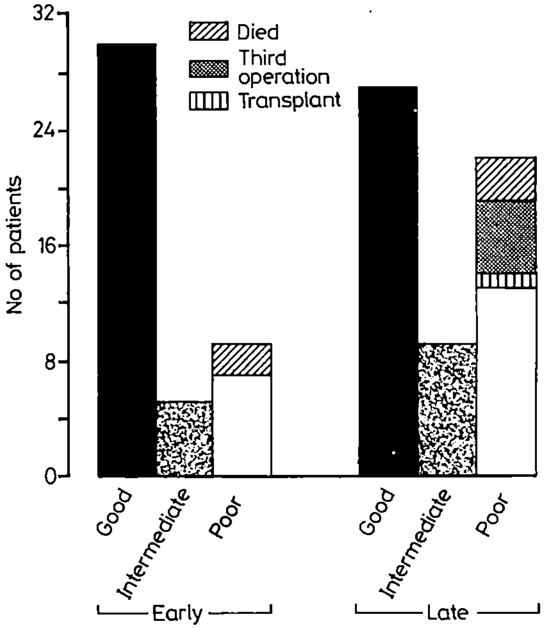

Fig. 2 *Comparison of outcome in patients with early (< 24 months) and late (> 24 months) follow up.*

Table 4 *Distribution of factors, which may be determined before reoperation, in the three groups divided according to the result of reoperation. Figures (except for age) indicate number of patients*

Condition	*No of patients*	*Outcome after reoperation*		
		Good	*Intermediate*	*Poor*
Total	102	57	14	31
Age (y)	102	52·9	52·5	52·1
Male	93	51	14	28
Diabetes	9	2	2	5
Smoking	34	19	7	8
Hypertension	20	11	1	8
Hypercholesterolaemia	29/53*	15/28	9/10	5/15

*Number of patients with hypercholesterolaemia out of number of patients in whom serum cholesterol concentration was measured.

Table 5 *Distribution of features of first operations and reoperations among the three groups divided according to result of reoperation*

Surgical factors	*No of patients*	*Outcome after reoperation*		
		Good	*Intermediate*	*Poor*
Total	102	57	14	31
Endarterectomy:				
First operation	24	14	6	4
Reoperation	18	9	5	4
Mean number of grafts placed per patient (n=102):				
First operation		2·12	2·33	2·0
Reoperation		2·00	2·20	1·77
Revascularisation at reoperation (n=100):*				
Complete	61	34	10	17
Incomplete	39	21	4	14

*Not determined with certainty in two patients.

for recurrent angina were excluded, recurrence occurred at a mean interval of 25·4 (SD±22·5) months for those whose outcome was good and of 17·0 (19·9) months for those who fared poorly after reoperation. Patients in whom incomplete revascularisation was implicated as a cause for recurrence fared slightly better after reoperation than those whose first operations were considered complete.

Exercise tests were performed in 47 subjects at a mean interval after reoperation of 29·8 months. Twenty three patients achieved ≥450 kpm on the bicycle ergometer, and seven ≥ stage 3 of the modified Bruce protocol on the treadmill. Twenty four patients also had preoperative tests. After reoperation 10 patients achieved a higher workload, six the same, and eight only a lower maximum.

At follow up 53% of patients were receiving beta blocking drugs and 50% nitrates regularly.

Discussion

The majority of patients in this and other reported studies underwent reoperation for the persistence or recurrence of severe angina. The results of reoperation do not seem to have been compared with those of continuing medical management in this situation. Nevertheless, as angina had proved refractory to optimal medical treatment, often for many months, the symptoms would probably not have resolved spontaneously in an appreciable number of patients without reoperation. Reoperation can be performed with a relatively low mortality (Table 6), which it nevertheless higher than for first operations,[1] and the risk of complications also tends to be higher. The most notable problems relate to resternotomy, when a previously placed graft to the left anterior descending artery is at risk.[11 12] Up to 10% of patients may require further resternotomy for postoperative bleeding.[3]

Most patients in reported series derive benefit from further revascularisation, but often only a few gain complete relief from angina (Table 6). Our results are similar. Reoperation is usually regarded as a symptomatic measure, and it is therefore appropriate to assess the outcome in terms of patients' subjective description of their symptoms. This assessment does not always yield a clearly defined end point, and the patients' perception of their symptoms may also depend on many extraneous influences, such as depression or inappropriate expectations. For these reasons we attempted to make an objective assessment by formal examination of exercise performance, although we recognise that the maximum workload is also dependent on the patient's co-operation and enthusiasm. Table 7 shows the relation between the maximum exercise workloads achieved and the patient's subjective assessment of symptoms. It is a matter of interpretation which means of expressing the outcome is the more valid. Our exercise test data are incomplete. It was clinical policy at this centre not

Table 6 *Figures for survival and outcome after reoperation derived from series published between 1978 and 1983. Figures marked with + are percentages of surviving patients*

Centre	*No of patients in study*	*Mean follow up interval*	*Survival (%)*	*Minimal or no angina (%)*	*Satisfactory outcome (%)*
Cleveland[3]	500	5 yr	89	60	89
Houston[7]	168	6 yr	82	—	84+
Mayo Clinic[8]	106	43 mnth	91	28	63 (at 5 years)
Los Angeles[9]	79	32 mnth	86	38	71
Portland[10]	79	2 yr	95	—	88
Ottawa[11]	74	23 mnth	97	52	77
Stanford[12]	71	2·2 yr	89	27	59
Rotterdam[13]	53	3·5 yr	91	35	88
New York[14]	48	—	88	86	90+
Montreal[15]	43	30 mnth	95	—	85 (symptomatic patients)
Washington[16]	40	6 mnth to 6 yr	98	23	83
Hammersmith[17]	34	18 mnth	97	42	69

Table 7 *Comparison between the results of postoperative exercise testing and patients' subjective assessment of their symptoms after reoperation*

Symptomatic outcome	*Maximum workload (kpm (treadmill stage))*			
	300 (1)	*450 (2)*	*600 (3)*	*750 (>4)*
Good	5	7	9	6
Intermediate	1	4	2	—
Poor	6	4	3	—

to subject patients who had angina at rest to exercise testing, and many patients fell into this category. Many patients lived at considerable distance from the hospital and were not available for postoperative testing.

The position regarding symptomless patients, in whom angiography postoperatively shows unsatisfactory revascularisation, is less clear. Reported results are conflicting.[11 15] At present the usual clinical practice is to consider reoperation only in patients with symptoms.

The age and sex distribution and incidence of diabetes, smoking, hyperlipidaemia, and hypertension are typical of those reported elsewhere.[7] An appreciation of any factors which presage a good or poor outcome would be valuable to clinical management. It was disappointing in this study that no such factors clearly emerged. We failed to find any influence of the cause of recurrent angina after first operation on outcome, which is in agreement with several other studies,[8-10] although Laird-Meeter *et al* found that patients with failed grafts fared worse than those with progressive disease.[13] The data shown here of our current and expanded experience do not confirm the earlier observation[4] that patients who receive grafts only to previously ungrafted vessels fare better than those requiring grafts to vessels already grafted. We noted a slight trend for a shorter interval to recurrence of angina to correlate with a poorer outcome, and a significant such correlation is reported by Krause *et al.*[10] This observation could be explained by postulating more aggressive coronary disease in these patients. Patients whose recurrence is attributable to graft failure tend to have an earlier return of angina than those whose cause is progressive disease,[3 17] but in all cases angiography remains mandatory for anyone in whom reoperation is contemplated.

An assessment of the completeness of revascularisation at reoperation did not help determine outcome, perhaps because vessels considered to be too small to graft were not included in the analysis. Such small vessels might still be responsible for further symptoms.

Patients requiring reoperation have a high incidence of risk factors.[18] Although these do not usually exert any adverse influence on outcome after reoperation,[10] it seems prudent to give firm advice to abstain from smoking. We found diabetes over-represented in the group who fared poorly after reoperation, but the numbers are too small to derive statistical inference. Diabetes has a mildly deleterious effect on outcome after primary revascularisation, which is not considered sufficiently adverse to disbar diabetics from surgery.[19 20]

Our results in patients with longer follow up are less encouraging (Fig. 2). The interval over which patients are studied may not be the only determinant of outcome. Those with longest follow up are also those reoperated on earlier in the series, when experience in the procedure was less and selection criteria may have varied. The earlier patients (more than two years' follow up) had fewer grafts inserted at their first operations (mean 1·92/patient) than the later patients (2·35/patient). For these later patients to receive only grafts to ungrafted vessels was unusual. Reported experience of long term results after reoperation remains limited (Table 6).

This report includes a relatively high proportion of single vein graft procedures (27) at primary revascularisation, but 10 of these patients required more than one graft. Most of these incomplete operations date from early in the series, and current practice is to attempt complete revascularisation. There is theoretical concern that patients who require surgery for intractable symptoms with single vessel disease may have a poorly developed collateral circulation which makes them susceptible to recurrence of angina if their sole graft ceases to function. In practice patients with single grafts are more prone to recurrence.[3] In our report only two patients underwent reoperation when failure of a single graft was the only cause of returning angina. Our experience is that the main risk for patients with single grafts is the development or progression of stenoses in ungrafted vessels. In future angioplasty may defer the need for surgery until multiple grafts are required.

The strategy for the surgical management of coronary artery disease must take cognisance of the increasing likelihood of recurrent angina as time elapses after initial revascularisation. In this study we detected a similar trend after reoperation. It seems intuitively probable that factors that militate against a successful outcome to the first procedure may be operative after further surgery. It is premature to establish the role of third procedures, although results can be expected to be less promising than after first or second operations. Not all patients with recurrent angina will be suitable for reoperation; experience relates only to those in whom surgery appears technically feasible, which may comprise only a third of the total.[13] Progression of minor stenoses to those of haemodynamic importance has been reported,[9] and this evidence has been cited to indicate the need to bypass them at first operation to obviate the need for later revascularisation. Current practice is to place more grafts than was formerly usual.

Surgical management may be viewed as a series of palliative procedures, initially highly successful, in an inexorably progressive disease. The reasonable expectation of further improvement of symptoms, possibly for many years if severe angina recurs, remains a worthwhile objective, which can be achieved at low risk by reoperation when angiography shows that surgery is technically feasible.

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Abrupt withdrawal of atenolol in patients with severe angina

Comparison with the effects of treatment

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SUMMARY The effects of abrupt withdrawal of atenolol, a long acting cardioselective beta blocker, were studied in 20 patients with severe stable angina pectoris admitted to hospital for coronary arteriography. During the 144 hour postwithdrawal period no serious coronary events occurred. Mean and maximal daily heart rates rose steadily for at least 120 hours. No important arrhythmias were noted on ambulatory electrocardiographic monitoring. Treadmill exercise testing at 120 hours showed little reduction in the times to angina, ST depression, and maximal exercise when compared with those recorded at 24 hours. This deterioration was small when contrasted with the improvements in these indices produced by atenolol treatment in a similar group of patients not admitted to hospital.

No change in catecholamine concentrations or acceleration of the heart rate response to exercise occurred after atenolol withdrawal, suggesting that rebound adrenergic stimulation or hypersensitivity was absent or insignificant. Catastrophic coronary events after beta blockade withdrawal (the beta blockade withdrawal syndrome) have occurred almost exclusively in patients taking propranolol, many of whom had unstable angina at the time of withdrawal. This study showed that in patients with stable angina, even when severe, the abrupt withdrawal of atenolol can be expected to result in only minor clinical consequences. The risk to any patient of so called rebound events after withdrawal of beta blockade seems to be related to both the clinical setting and the agent being used.

Beta adrenergic blocking agents are widely used in patients with ischaemic heart disease, both in the treatment of angina and for secondary prevention of myocardial infarction.[1 2] While patients with angina would be expected to experience some symptomatic deterioration on withdrawal of beta blockade a few have suffered dramatic or catastrophic coronary events after beta blockade withdrawal; hence a specific beta-blockade withdrawal syndrome has been reported.[3–5]

Between 1973 and 1976 about 33 such cases were reported, all related to propranolol. These included patients who developed acute coronary insufficiency, acute myocardial infarction, or sudden death up to three weeks after propranolol withdrawal.[6–8] Although numerous beta blocking agents have been introduced since then, very few additional cases of the withdrawal syndrome have been reported.[9]

Atenolol is a widely used, long acting, water soluble, cardioselective beta blocker which has not as yet been associated with a withdrawal syndrome. Although this may be due to a lack of reporting as a result of general acceptance of the syndrome, the relatively long period for which beta blockade persists after atenolol withdrawal may possibly protect against these so called rebound events.[10]

This study was designed to document the effects of abrupt atenolol withdrawal on angina severity and exercise tolerance in a high risk group of patients admitted to hospital (group 1). Evidence of increased sympathetic output, which has been seen after beta blockade withdrawal in some hypertensive patients,[11] was sought by recording daily changes in heart rate and catecholamine concentrations for 120 hours after atenolol withdrawal.

To determine whether the adverse effects of

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atenolol withdrawal were disproportionate to its therapeutic effect, and thus consistent with a true rebound phenomenon, the changes in exercise test indices which relate to the severity of myocardial ischaemia—that is, times to angina and ST segment depression and total exercise time—which followed atenolol withdrawal were compared with those produced by atenolol in a similar group of angina patients not admitted to hospital (group 2).

Of the various mechanisms proposed for the beta blockade withdrawal syndrome, rebound adrenergic hypersensitivity has received the greatest attention.[11–13] In a study of euthyroid and hyperthyroid subjects this phenomenon was seen at 4–7 days after atenolol withdrawal.[14] To examine its possible clinical significance in patients with angina the rate of acceleration of heart rate during exercise, which in part relates to sympathetic responsiveness, was measured five days after withdrawal and compared with that in patients in group 2.

Patients and methods

Twenty patients with chronic stable angina (group 1) were selected for the study, which was to be carried out during hospital admission for coronary arteriography with a view to surgery. They were aged 36–60 (mean age 50) years; 19 were male and one was female. All had been receiving beta blockade for at least three months, and despite treatment with their current regimen of atenolol 100 mg daily all complained of class III or IV (NYHA classification) angina. Hypertensive patients and patients with unstable angina were excluded. No additional antianginal medication other than sublingual glyceryl trinitrate had been taken during the two weeks before admission.

Patients were admitted on day 0, when they received atenolol 100 mg at 0900. No further dose was given until day 6, 144 hours later, before discharge. They were questioned daily regarding any change in their angina pattern. Coronary arteriography was performed on day 3.

AMBULATORY MONITORING

Continuous ambulatory electrocardiographic monitoring (lead CM5) was performed from day 1 to day 5—that is, from 24 to 120 hours after the last dose. Oxford Medilog 1 recorders were used with Reynolds Pathfinder analysis. Total, peak, and mean heart rates for each 24 hour period were calculated, together with the total number of extrasystoles and ST segment trends.

EXERCISE TESTING

Maximal treadmill exercise testing using a modified Bruce protocol and 12 lead electrocardiographic monitoring was performed at 24 and 120 hours after the last dose of atenolol. The electrocardiogram was recorded at rest and after each minute of exercise. Arm blood pressure was recorded at one minute intervals using a sphygmomanometer.

These two tests were performed so that changes in exercise performance and threshold for myocardial ischaemia resulting from atenolol withdrawal might be measured quantitatively. Without an initial exercise test before treatment with atenolol it would, however, be impossible to state with certainty whether a deterioration in exercise tolerance between days 1 and 5 represented a true rebound phenomenon or simply the removal of a beneficial effect. Since a pretreatment test was not performed, the exercise test results of these patients (group 1) were compared with those in a group of 28 patients with stable class II to IV angina who were being given atenolol 100 mg daily as their only treatment (group 2). Using the same exercise protocol, these patients were exercised before treatment and again after four weeks of treatment, the second test being at two hours after a morning dose. The changes in exercise performance in group 2 thus reflect the objective benefits of atenolol treatment and provide a valid yardstick with which to compare the deleterious effects of withdrawal. The Table shows the clinical features of the two groups.

HEART RATE CHANGES DURING EXERCISE

The rate of acceleration in heart rate was defined as the absolute change in heart rate during exercise (maximum rate minus resting rate) divided by the number of minutes exercised. This value in beats per minute was calculated for group 1 patients on day 5 and for group 2 patients before treatment.

Table *Clinical features of 20 patients in whom atenolol was withdrawn (group 1) and in 28 starting treatment with atenolol (group 2)*

	Sex (M/F)	*Age (yr)*		*Grade of angina*			
		Mean	*Range*	*I*	*II*	*III*	*IV*
Group 1	19/1	50	36–60	0	0	4	16
Group 2	24/4	52	32–61	0	7	6	15

CATECHOLAMINE EXCRETION

Plasma noradrenaline concentration was measured daily from day 1 to 5 in the first seven patients by the radioenzymatic method of Henry *et al,*[15] both after resting supine for 30 minutes and after tilting at 65° for five minutes.

Twenty four hour urinary excretion of catecholamines was measured in 11 patients by the trihydroxyindole method; the amines were extracted with alumina at pH 8·5 and the final fluorescence was read in a Perkin-Elmer spectrofluorimeter. The excretion of vanilmandelic acid in the urine was measured in these patients by the spectrophotometric method of Pisano *et al.*[16]

STATISTICAL ANALYSIS

All statistical analysis was by Students paired *t* test for within group comparisons and by the unpaired *t* test for comparisons between groups 1 and 2.

Results

SYMPTOMATIC CHANGES (GROUP 1)

No serious complication arose during the withdrawal period, and no patient required the early reintroduction of beta blockade. No patient complained of so called withdrawal symptoms such as palpitation, headache, or anxiety.[12] Three patients noticed a worsening of their angina, and one had a 30 minute episode of rest pain on day 5; all three experienced very easily induced angina on day 1—that is, by the fourth minute of the exercise protocol.

Coronary arteriography was performed without incident on day 3. Eighteen patients had multivessel disease and two had single vessel disease.

AMBULATORY MONITORING (GROUP 1)

Analysis of peak and mean heart rates for each 24 hour period was possible in 10 patients (Fig. 1) A steady day to day increase was seen, with no rebound tachycardia.

The number of ventricular extrastysoles tended to increase as beta blockade disappeared (from 255 (64) (mean (SD)) on day 2–3 to 492 (954) on day 5–6 ($p<0\cdot05$)). No episodes of tachyarrhythmia were seen.

Analysis of ST segment changes was possible in nine patients. Two had more ST depression on day 5–6 than on day 2–3 but none showed a stepwise trend of worsening ST depression.

EXERCISE TESTING (GROUPS 1 AND 2)

Figure 2a shows the exercise times to angina and to 1 mm ST depression and the total duration of exercise on days 1 and 5 in group 1. In the group as a whole there was a small significant reduction in the time to ST depression on day 5 but no change in the time to angina or the total exercise time. Individually, eight patients showed $>10\%$ deterioration in the exercise time to both angina and ST depression on day 5, but in no instance was this particularly pronounced. Seven patients showed no deterioration in either index, while two patients showed improvement in both.

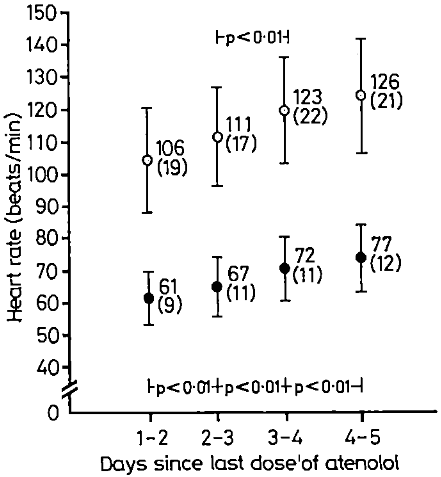

Fig. 1 *Peak (○) and mean (●) daily heart rates in 10 patients (group 1) after atenolol withdrawal recorded by continuous ambulatory electrocardiographic monitoring. Values are mean (SD).*

Figure 2 also shows the results of exercise testing in the patients in group 2, performed before and during atenolol treatment. These twenty eight patients derived a highly significant benefit from atenolol, which in every respect exceeded the deterioration which followed atenolol withdrawal in the patients in group 1.

Heart rate changes

The mean resting heart rate in group 1 patients before exercise testing on day 5 was 79 (13) beats/min compared with 72 (13) beats/min in untreated group 2 patients (NS). During exercise testing heart rates rose by a mean of 8·8 (7·4) beats/min in group 1 and by 10·0 (5·3) beats/min in group 2 (NS). One patient in group 1 was exercised for only 1·3 minutes on day 5 compared with 3·0 minutes on day 1; on both occasions he had an exaggerated heart rate response to exercise (17 beats/min on day 1 and 35 beats/min on day 5). Angina developed within the first minute of both tests. This patient had very severe coronary disease with impaired left ventricular function and died during aortocoronary bypass surgery three weeks later. If he is excluded from the analysis then a significantly slower rate of rise in heart rate occurred

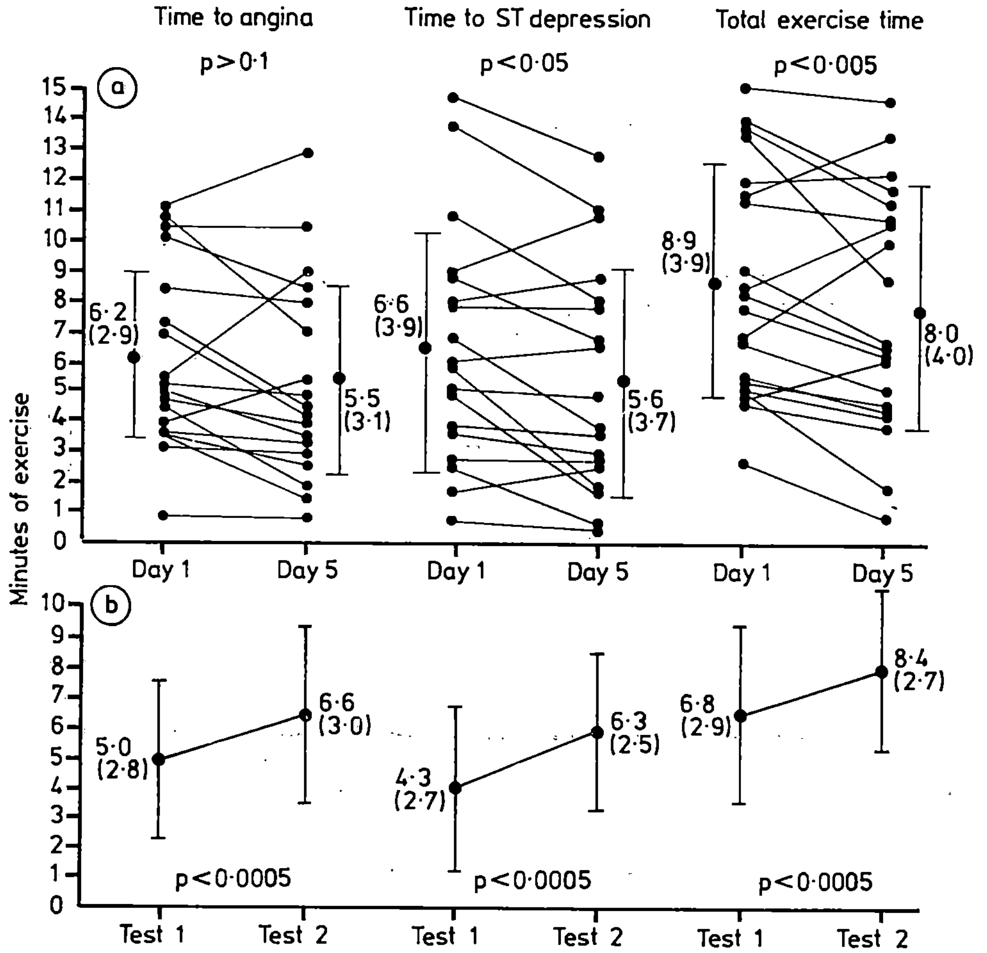

Fig. 2 *Results of treadmill exercise testing in (a) 20 patients (group 1) performed 24 hours (day 1) and 120 hours (day 5) after atenolol was last taken (individual values and mean (SD) values are shown; values for only those 18 patients who developed angina or ST depression on both days 1 and 5 are given) and (b) 28 patients (group 2) performed before (test 1) and during treatment with atenolol 100 mg daily (test 2). Test 2 took place after four weeks' treatment two hours after a morning dose. Values are mean (SD).*

after atenolol withdrawal than in the patients in group 2 (7·4 (4·3) *vs* 10·0 (5·3) beats/min, $p<0\cdot05$).

CATECHOLAMINE EXCRETION

Figure 3 shows the plasma noradrenaline estimations. No trend of rising or falling concentrations was seen. Day to day variations during recumbency and tilting fell within the range of variability found in a small group of healthy, untreated subjects, whose noradrenaline concentrations were measured on two separate days (Fig. 4). Thus mean concentrations in seven patients in group 1 showed day to day variations of up to 35% (recumbent) and 6% (tilted), while individual variability of up to 73% and 25% respectively was observed in the healthy subjects. One patient showed a 100% increase in noradrenaline concentration during recumbency on the day of coronary arteriography, compared with the previous day's concentration but little further rise on tilting. On every other day his recumbent concentration was around 500 ng/l. This patient explains the high mean value on day 3.

Figure 5 shows the urinary catecholamine and vanilmandelic acid excretions. Again, no significant changes followed atenolol withdrawal.

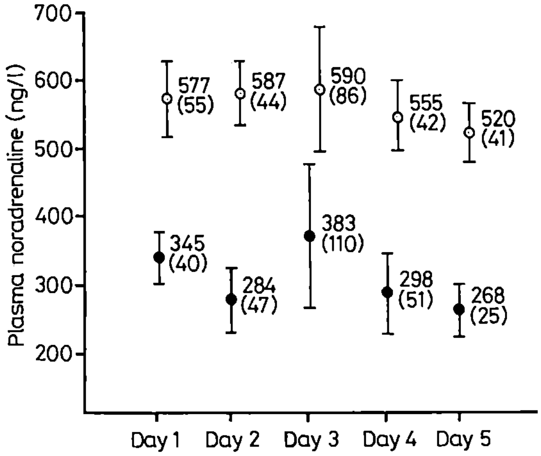

Fig. 3 *Plasma noradrenaline concentrations measured daily for five days after atenolol withdrawal in seven patients in group 1, supine (●) and after tilting (○) at 65° for five minutes. Values are mean (SEM).*

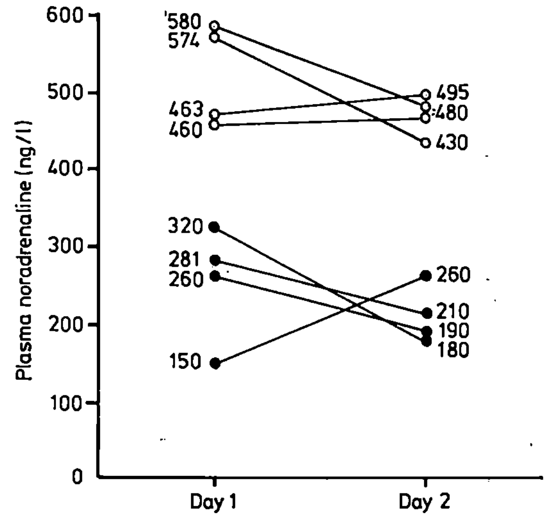

Fig. 4 *Plasma noradrenaline concentrations measured in four healthy, untreated subjects on two separate days supine (●) and after tilting (○) at 65° for five minutes.*

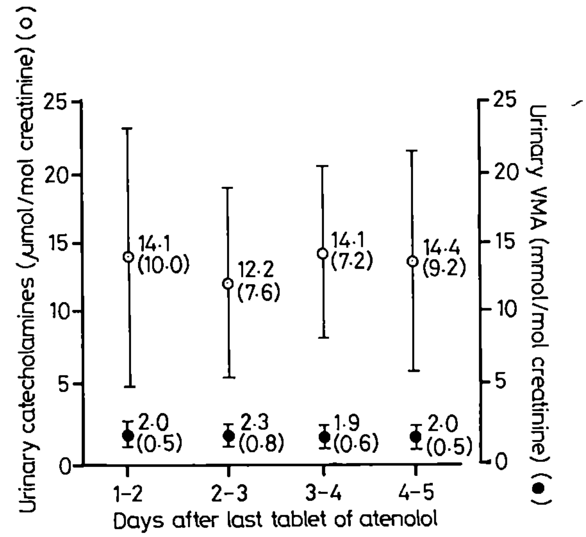

Fig. 5 *Twenty four hour urinary catecholamine (○) and vanilmandelic acid (VMA) (●) excretion measured daily in 11 patients for five days after atenolol withdrawal. Values are mean (SD).*

Discussion

Many of the case reports describing the beta blockade withdrawal syndrome concerned patients with worsening or unstable angina at the time of withdrawal.[4] This contrasts with planned studies of beta blockade withdrawal such as the present study, which have for ethical reasons excluded such patients. Thus in one prospective series in 100 consecutive patients admitted for coronary arteriography propranolol was withdrawn for a mean period of 39 hours.[17] Ninety patients reported no worsening of angina, and coronary events were no more frequent than in the period preceding withdrawal. In a retrospective study the morbidity among 55 inpatients in whom propranolol had been withdrawn for a mean of 80 hours was no greater than in 47 control patients who continued to take propranolol.[18] Since propanolol is of proven value in treating stable angina[19] the absence of any apparent symptomatic deterioration in such inpatients is presumably the result of the reduction in physical activity which follows admission to hospital. It could be argued that the postwithdrawal periods in these two studies were too short, since propranolol withdrawal phenomena appear to be most common between four and seven days after stopping treatment.[4 12] Our study endeavoured to assess symptomatic changes objectively using two standardised exercise tests; the first at a time when therapeutic beta blockade was present and the second during the period when rebound hypersensitivity and hence symptomatic deterioration should have been most pronounced.[12 14] We used a postwithdrawal period of 144 hours, which with hindsight could perhaps have been made even longer since at 96 hours after the last dose there was evidence of persisting beta blockade on ambulatory heart rate analysis.

Comparison of the two exercise tests showed a surprisingly small symptomatic deterioration after atenolol withdrawal: of the times to angina and ST depression and the total exercise time, only the time to ST depression was significantly reduced. This was in sharp contrast to the improvement in each of these exercise test indices produced by atenolol treatment in the patients in group 2. This disparity was not due to an absence of effective beta blockade on day 1, since heart rates both before and at peak exercise were much lower on day 1 than on day 5 (61 (8) and 114 (19) beats/min respectively on day 1 *vs* 79 (13) and 131 (19) on day 5, $p<0\cdot01$); neither was the symptomatic status of the two groups of patients very dissimilar, as judged by their exercise test performances without atenolol (compare Figs. 2 and 3). More probably, the apparent discrepancy between the effects of treatment and withdrawal resulted from the difference in the timing of exercise tests in the two groups (24 hours after atenolol in group 1 and two hours after atenolol in group 2),[20] together with a small training effect and some possible persistence of beta blockade on day 5. In the event, it seems reasonable to conclude that atenolol withdrawal led to a lowering of the exercise threshold for myocardial ischaemia which was certainly no greater than the removal of its therapeutic effect and which therefore was not in keeping with a rebound phenomenon.

It has been suggested that withdrawal phenomena might be prevented by a gradual tailing off of the dose of beta blocker.[4 8 21] This study and others[22–24] show that even after withdrawal of shorter acting agents such as propranolol there is a gradual increase in heart rate over several days, suggesting that a gradual reduction in dosage is unnecessary.

The mechanisms by which beta blockade withdrawal might cause catastrophic coronary events remain controversial. The chief action of these agents in angina is to reduce myocardial oxygen demand, mainly by reducing heart rate and double product.[24–26] It has reasonably been suggested that by causing a rise in these determinants of oxygen consumption beta blockade withdrawal could cause myocardial ischaemia and necrosis even under resting conditions.[3 4 8] In the present study, however, myocardial ischaemia, as shown by angina and ST segment depression, developed at considerably higher heart rates (up to 35 beats/min) and double products on day 5 than on day 1. This effect of atenolol (and other beta blockers[27]) of reducing considerably the heart rate at which angina develops was even more pronounced in the group 2 patients (97 (15) beats/min during treatment *vs* 120 (15) beats/min before treatment, $p<0\cdot0001$). Therefore, while beta blockade withdrawal increases the basal heart rate, the rate at which ischaemia develops is reset at a higher level; hence, in some patients atenolol withdrawal produced no deterioration, just as in some patients beta blockade produces no objective benefit.[28–30]

A second mechanism proposed for withdrawal phenomena is rebound hypersensitivity of cardiac beta receptors to circulating catecholamines.[11–13] While hypersensitivity to infused isoprenaline has been seen after propranolol withdrawal in hypertensive[12] and normal[11] subjects other studies have not confirmed this phenomenon.[31 32] At the time when rebound hypersensitivity is said to be present after atenolol withdrawal[14] no acceleration of the heart rate response with exercise was seen in our patients in group 1 when compared with group 2. In the one patient who had an exaggerated response the cause was almost certainly exercise induced pump failure[33] since it was present on day 1 as well as on day 5. An exaggerated heart rate response to exercise was observed in five normal subjects at 66 hours after propranolol withdrawal, but not when these subjects were withdrawn from atenolol.[34] Thus although adrenergic hypersensitivity may occur after atenolol withdrawal by mechanisms which increase sympathetic drive,[14] it appears to exert no influence on the heart rate response during normal physical activity.

An increase in the concentrations of circulating catecholamines after beta blockade withdrawal has been found in some hypertensive patients[12] while in others the concentrations fell[35] or did not change.[36] In a normotensive group of patients with angina (a group resembling our own) Lindenfeld *et al* found no change in plasma noradrenaline concentration after propranolol withdrawal[32]; similarly, in a small group of normal normotensive subjects no change in plasma noradrenaline concentrations followed withdrawal of either propranolol or atenolol.[34] Alterations in concentrations of circulating catecholamines after beta blockade withdrawal may therefore be peculiar to hypertensive subjects, in whom abnormal sympathetic activity has been reported.[37]

Thus the abrupt withdrawal of atenolol in 20 patients with severe angina produced minor clinical effects which were no greater than those expected from the removal of its therapeutic effect and was unaccompanied by evidence of sympathetic overactivity or adrenergic hypersensitivity. Serious coronary events after beta blockade withdrawal have occurred almost exclusively in patients with severe or worsening angina who were taking shorter acting agents, and in such patients the abrupt stopping of treatment outside hospital would obviously be unwise. While rare idiosyncratic reactions to beta blockade may have occurred, and could never be ruled out by a prospective study, this study shows that the clinical consequences of abrupt atenolol withdrawal are usually minor and predictable corresponding with a gradual disappearance of beta blockade over several days. In patients with less severe or no angina atenolol withdrawal would therefore be expected to carry no appreciable risk of precipitating a coronary event.

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Comparison of ventricular emptying with and without a pressure gradient in patients with hypertrophic cardiomyopathy

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SUMMARY Thirty three patients with hypertrophic cardiomyopathy were studied to determine whether the presence of an intraventricular pressure gradient impaired left ventricular emptying. Patients with resting gradients had a higher mean left ventricular ejection fraction (92 (6·4)%) than patients without a resting or inducible pressure gradient (75·5 (9)%). The rate and degree of emptying increased when gradients >85 mm Hg were induced in two patients with insignificant mitral regurgitation.

If the induced gradients had been the result of obstruction a decrease in the rate or degree of ventricular emptying would be expected. Higher ejection fractions in patients with intracavitary pressure gradients as well as enhanced rate and degree of left ventricular emptying with induced gradients are inconsistent with outflow obstruction. These findings support the concept that cavity obliteration is responsible for the pressure gradient in these patients with hypertrophic cardiomyopathy.

There is a controversy about the importance of intraventricular pressure gradients in patients with hypertrophic cardiomyopathy. The presence of intracavitary left ventricular pressure gradients in patients without intraoperative or postmortem anatomical evidence of obstruction led Brock to the concept of a "functional obstruction of the left ventricle" in the late 1950s.[1 2] Although the precise site of functional obstruction was initially thought to be a muscular sphincter or "contraction ring",[1–6] systolic anterior motion of the anterior mitral leaflet with apposition of the leaflet with the ventricular septum has been generally accepted as the anatomical basis for the pressure gradient and for an impediment to egress of blood from the left ventricle.[7–12] The ability of the ventricle to empty rapidly in the presence of outflow tract obstruction has been attributed to late systolic mitral regurgitation.[12]

An alternative non-obstructive basis for the intracavitary pressure gradient in hypertrophic cardiomyopathy derives its theoretical premise from the work of Gauer and Gauer and Henry who recorded gradients within the hyperkinetic and hypovolaemic left ventricle in experimental animals during haemorrhagic shock and during the application of negative gravitational forces.[13 14] This non-obstructive mechanism (cavitary obliteration or elimination) has been shown to be responsible for intracavitary left ventricular gradients in experimental animals and in man during various conditions which increase the contractile force or diminish the filling volume and peripheral resistance or both (for example, catecholamines,[15] septic shock,[16] amyl nitrite inhalation combined with the Valsalva manoeuvre or post-extrasystolic potentiation.[17]) In the Gauer phenomenon, a pressure gradient develops within a hyperdynamic ventricle. The outflow tract shares the same systolic pressure as the aorta beyond, since they are in free communication. The left ventricular body generates a higher pressure as it progressively separates itself from the outflow tract while obliterating its cavity.

These diametrically opposed explanations of the pressure gradient in hypertrophic cardiomyopathy have not been satisfactorily resolved. The purpose of

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Table 1 *Haemodynamic findings in 33 patients with hypertrophic cardiomypathy. Values are mean (SD)*

	Group 1	*Group 2*	*Group 3*	*All groups*
Mean (SD) age (yr)	60 (12)	57·7 (19)	50·5 (19)	55 (18)
Sex (M/F)	5/3	6/4	7/8	18/5
Mean right atrial pressure (mm Hg)	4·6 (4·9)	4·4 (2·9)	4·2 (2·4)	4·3 (3)
Pulmonary artery pressure (mm Hg)				
Systolic	28 (8)	27 (8)	30 (7)	29 (7)
Diastolic	13 (5)	12 (6)	12 (4)	12 (5)
Left ventricular end diastolic pressure (mm Hg)	15 (7)	19 (9)	15 (5)	16 (7)
Left ventricular systolic pressure (mm Hg)*	121 (21)	142 (25)	189 (28)	158 (39)
Cardiac index (l/min per m^2)	2·4 (0·4)	2·9 (1·0)	3· (0·9)	2·8 (0·8)
Resting gradient (mm Hg)	0	0†	77 (36)	
Inducible gradient (mm Hg)	0	93 (42)	140 (33)	

*Group 1 < group 2 < group 3 ($p < 0·05$).
†Three patients had resting gradient ≤ 15 mm Hg.

the current investigation was to use quantitative left ventricular angiography in patients with hypertrophic cardiomyopathy to study the relation between the pressure gradient and the ability of the ventricle to empty itself. Since previous investigations into the rate of left ventricular emptying have compared patients with hypertrophic cardiomyopathy with normal control subjects or patients with aortic stenosis,[18-21] we particularly wanted to study the effect of an induced pressure gradient on left ventricular emptying in selected patients with hypertrophic cardiomyopathy without significant mitral regurgitation so that each patient served as his own control.

Patients and methods

Thirty three patients (18 men, 15 women mean (SD) age 55 (18) years) with clinical, echocardiographic, haemodynamic, and cineangiographic evidence of hypertrophic cardiomyopathy were classified into three groups on the basis of the absence of a resting or inducible intraventricular gradient (group 1), an inducible gradient (group 2), and a resting gradient of >25 mm Hg (group 3).

CINEANGIOGRAPHY

Cineangiography was performed with left ventricular injections of 0·5 to 0·8 ml/kg of contrast medium in 2–3 s, recorded at 30 to 60 frames per second on 35 mm film. A calibration object was filmed at the plane of the mid ventricle for quantitation of volume. Ventricular volume was determined by the Kennedy modification of the Dodge area-length formula for the right anterior oblique projection.[23] The ejection fraction was calculated in all 33 patients from normal sinus rhythm beats which did not follow premature ventricular contractions.

Table 2 *Severity of mitral regurgitation in 33 patients with hypertrophic cardiomyopathy. Figures are numbers of patients*

	*Degree of mitral regurgitation**				
	0	*1+*	*2+*	*3+*	*4+*
Group 1 (n=8) (no gradient)	4	2	1	1	0
Group 2 (n=10) (provokable gradient)	4	5	1	0	0
Group 3 (n=15) (resting gradient)	2	7	4	2	0

*From Grossman.[22]

The left ventricular cineangiograms of two of the patients (cases 1 and 2) in whom a pressure gradient could be induced were analysed in more detail. These patients were selected because of the absence of significant mitral regurgitation and because the edges of the angiographic silhouettes were clearly delineated permitting reproducible frame by frame volume determinations. These two patients had angiograms recorded during the absence of an intraventricular pressure gradient and after a significant gradient (>85 mm Hg) had been induced. Neither of these patients had significant (>1+) mitral regurgitation in that the atrium was only faintly opacified during systole and cleared completely with each diastole.[22] Frame by frame determinations of ventricular volume also permitted a correlation of pressure and volume.

In the frame by frame analysis of the cineangiograms of one patient (case 1) two or more cardiac cycles were plotted to ensure reproducibility. There was a <10 ml difference between matched frames at the same phase of the cardiac cycle, and the filling and emptying slopes of each beat could be superimposed. A gradient was induced with an infusion of sodium nitroprusside sufficient to reduce the systolic arterial pressure to 120 mm Hg, which was this patient's normal resting pressure. The timing of systolic anterior motion-septal contact was determined in this patient from the left anterior oblique projection.[24] A postectopic beat phenomenon induced a gradient of 110 mm Hg in one patient (case 2) who had no gradient at rest.

STATISTICAL ANALYSIS

A statistical analysis of the differences in left ventricu-

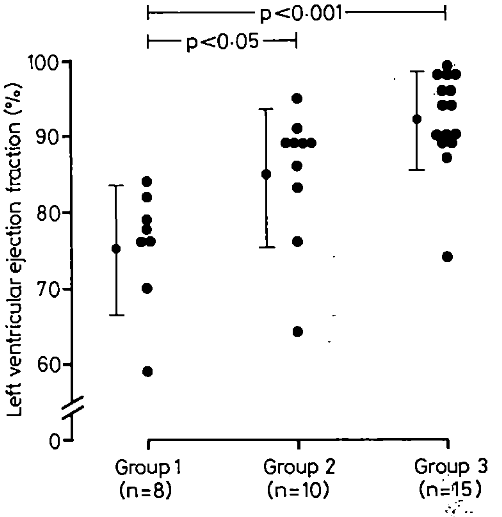

Fig. 1 *Angiographic left ventricular ejection fractions in 33 patients with hypertrophic cardiomyopathy with no gradient (group 1), an inducible gradient (group 2), and a resting gradient (group 3).*

lar ejection fraction between the three groups was performed using a one way analysis of variance.[25] Since the three groups did not come from the same sample linear contrasts were performed using the Boneferoni correction for multiple comparisons assuming a pooled variance.[26] Group comparisons of haemodynamic findings were performed using the Tukey method and the BMDP statistical package.[26] All values are expressed as mean (one standard deviation).

Results

There was no significant difference in age, right heart pressures, left ventricular end diastolic pressure, degree of mitral regurgitation, or cardiac index between groups 1, 2, and 3 (Tables 1 and 2).

Figure 1 shows the resting left ventricular ejection fractions for the three groups. Group 3 had a significantly higher mean ejection fraction (92 (6·4)%) than group 1 (75·5 (9)%, $p<0·001$). Similarly, group 2 had a higher ejection fraction (85 (9)%) than group 1 ($p<0·05$). Thus the group with the highest mean ejection fraction had resting pressure gradients, the group in whom gradients could be induced had an intermediate mean value, and those with no gradient had the lowest mean value. Five group 2 patients had ejection fractions calculated during control and induction of a pressure gradient, and each had an increase during the gradient from 2% to 9%. All three groups had significantly higher ejection fractions than the normal range (60 (8)%) for our laboratory ($p<0·05$).

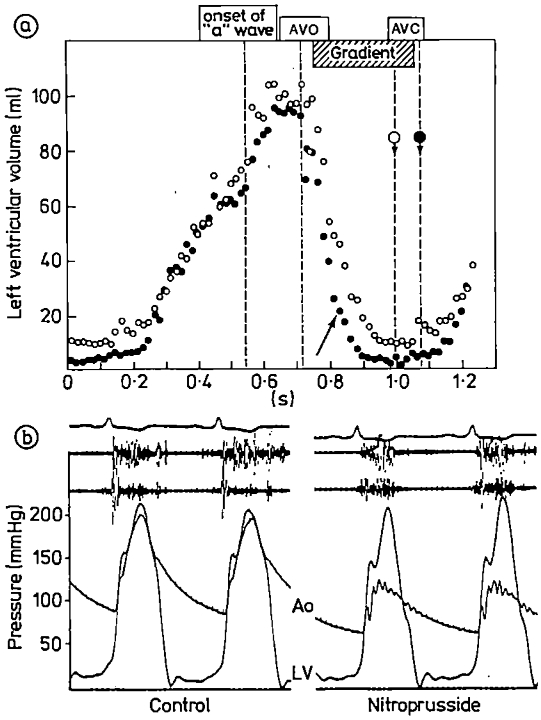

Fig. 2 *Case 1: angiographic frame by frame data (a) and left heart pressures (b) during control (no gradient) and during nitroprusside infusion (87 mm Hg gradient). (a) The left ventricle empties more rapidly and completely (ejection fraction rose from 89 to 94%) and achieves a systolic volume of 5 ml well before aortic valve closure (AVC) (solid dot and arrow). The onset of systolic anterior motion-septal contact from the left anterior oblique cineangiogram is indicated by the inclined arrow. The aortic valve closed later in the gradient study owing to delayed relaxation of the ventricle. (○) the angiographic volumes without a gradient and (●) with a gradient. AVO, aortic valve opening. (b) Transseptal left ventricular and retrograde aortic pressures are shown with electrocardiograms and phonocardiograms. After sodium nitroprusside infusion, no change in heart rate occurs but a 87 mm Hg gradient develops between the left ventricle (LV) and aorta (AO), with the left ventricular systolic pressure remaining constant.*

Figures 2 and 3 show the haemodynamic, volumetric, and angiographic data from the patient in case 1 (group 2) before and after an 87 mm Hg pressure gradient had been induced with an infusion of sodium nitroprusside. This usually normotensive patient had a hypertensive response during cardiac catheterisation. The gradient resulted from a decrease in aortic pressure, while the left ventricular pressure and heart rate remained constant (Fig. 2b). The left ventricular ejection fraction increased from 89% to 94%. Frame by frame volume analysis shows that the rate and degree of emptying increased after the gra-

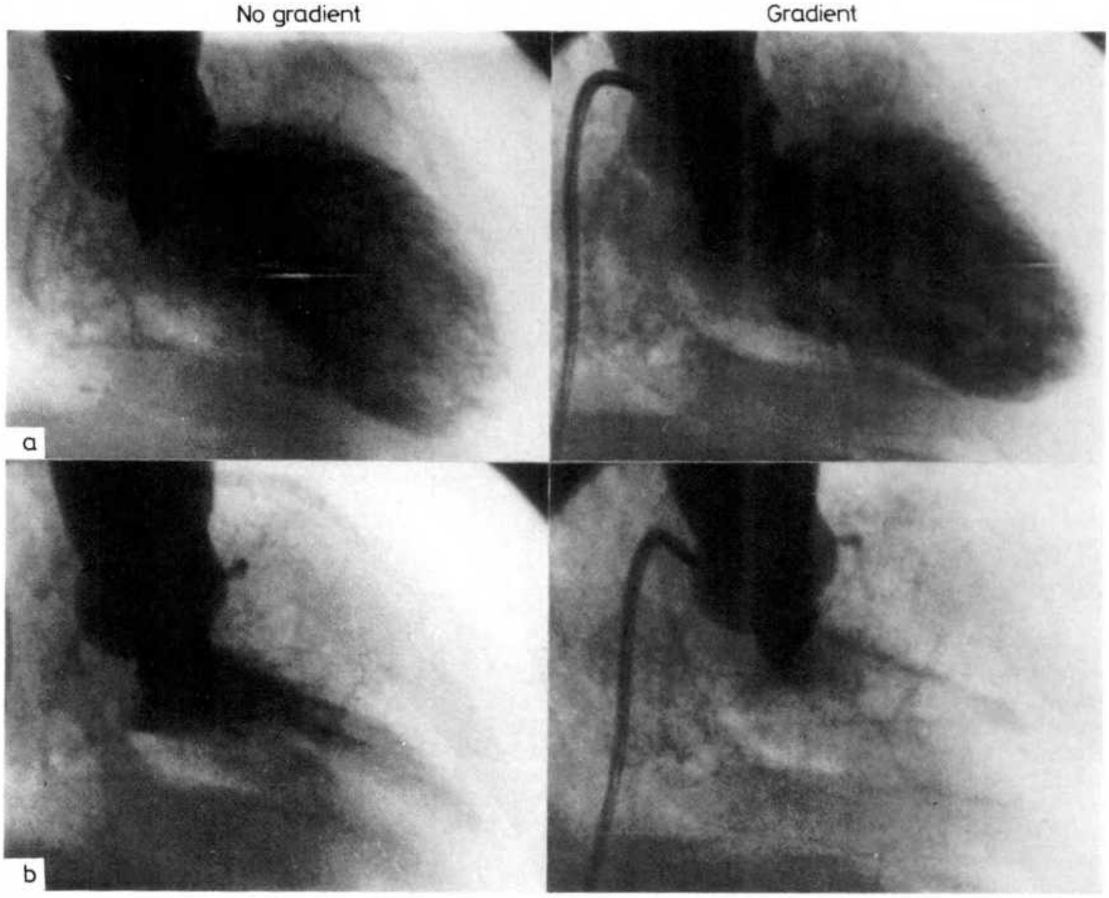

Fig. 3 *Case 1: angiograms during (a) end diastole and (b) end systole with no gradient and after an 87 mm Hg gradient was induced with nitroprusside. The degree of emptying during both studies caused obliteration of the cavity up to the level of the mitral valve and is increased after the gradient is induced.*

dient was induced (Fig. 2a). The ventricle continued to empty rapidly to a small volume in the presence of a pressure gradient and systolic anterior motion-septal contact.

Although the left ventricular emptying time (aortic valve opening to aortic valve closure) is prolonged in the presence of the pressure gradient, the left ventricle achieves a miniscule end systolic volume in half of the time available and maintains an isometric contraction for the last half of systole. The delay in aortic valve closure and mitral valve opening reflects a more prolonged state of contraction or a reduced rate of relaxation or both.

Figure 3 shows the end diastolic and end systolic frames from right anterior oblique ventriculograms. The end systolic volumes were calculated to be 10 ml (control) and 4 ml (nitroprusside), reflecting an excessive degree of emptying under both conditions. Insignificant (<1+) mitral regurgitation was seen during motion picture projection.

Figures 4 and 5 show the data from the study of the patient in case 2 (group 2). A postectopic beat and the following normal sinus beat were analysed. Before the left ventriculogram, premature ventricular contractions were induced by catheter manipulation, and the gradient between the left ventricle and femoral artery exceeded 110 mg Hg in the postectopic beat and the arterial pulse pressure decreased (Fig. 4b). Superimposition of the frame by frame plots of left ventricular emptying shows that there was more rapid and complete emptying during the postectopic beat in which the gradient was present (Fig. 4a). Trivial mitral reg-

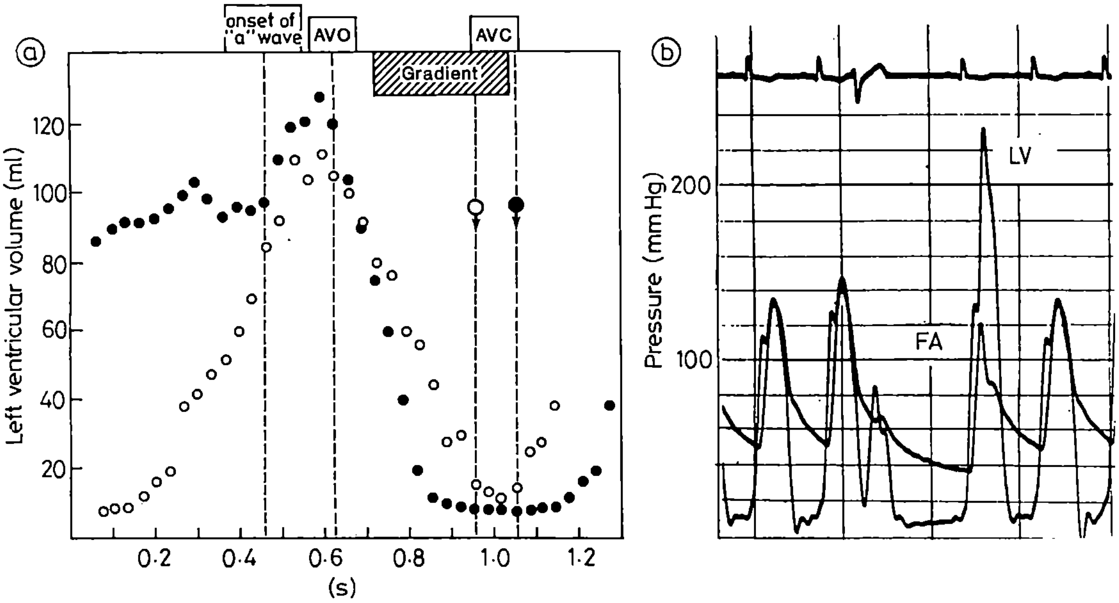

Fig. 4 *Case 2: angiographic frame by frame data (a) and left heart pressures (b) during a postectopic beat and the following sinus beat. (a) The ventricle empties more rapidly but has a delayed relaxation and aortic valve closure (AVC) in the postectopic beat. (○) no gradient, (●) with gradient; AVO, aortic valve opening. (b) Left ventricular (LV) and femoral artery (FA) pressures with an induced premature ventricular contraction with the same coupling interval as the premature beat during the angiographic study. The postectopic beat develops a gradient of 110 mm Hg, and the arterial pressure a "spike and dome" contour typical of hypertrophic cardiomyopathy and no increase in pulse pressure.*

urgitation was seen on analysis of the motion picture but is not evident in the still frames (Fig. 5). As in the previous case, aortic valve closure and the onset of ventricular filling were delayed in the gradient beat despite the fact that the ventricle achieved a greater degree of emptying earlier in systole.

Discussion

When there is an impediment to left ventricular outflow, as in valvar aortic stenosis, there is a transvalvar pressure gradient, a reduced rate of rise of the aortic systolic pressure, a prolonged ejection time, and a slow rate of ventricular emptying.[19] Despite the hindrance to outflow, the hypertrophied left ventricle in aortic stenosis may maintain a normal or increased ejection fraction, but when the obstruction is surgically relieved there is often an increase in the ejection fraction.[27]

The presence of a left ventricular outflow tract gradient and a prolonged ejection time in hypertrophic cardiomyopathy have been used as evidence of obstruction.[28 29] An explanation of the brisk aortic pulse contour characteristic of hypertrophic cardiomyopathy has been that the ventricular outflow tract is initially widely patent and becomes progressively obstructed during systole.[28] The rapid and complete emptying has been attributed to hyperfunction of the hypertrophied muscle and late systolic mitral regurgitation.[30]

It is acknowledged that the presumed obstruction in hypertrophic cardiomyopathy is not comparable to valvar aortic stenosis in that proponents of obstruction in hypertrophic cardiomyopathy have suggested that the early systolic rapid outflow followed by the absence of late systolic outflow is evidence of a "dynamic obstruction." Calculations of the effective orifice size using hydrodynamic formulas have indicated that the outflow orifice is widely patent early in systole when there is high flow and a small gradient and then progressively narrows throughout systole. Pierce and Morrow stated "in those instances where flow ceased and a pressure gradient persisted, one can only conclude that the subvalvular orifice closed completely prior to closure of the aortic valve."[28] If such an obstruction were imposed in midsystole, there would probably be an abrupt change in the rate of left ventricular emptying, but the emptying curves in the present study were not slowed when the gradient was present nor was there a significant increase in the degree of mitral regurgitation to explain the rapid and complete emptying in these cases.

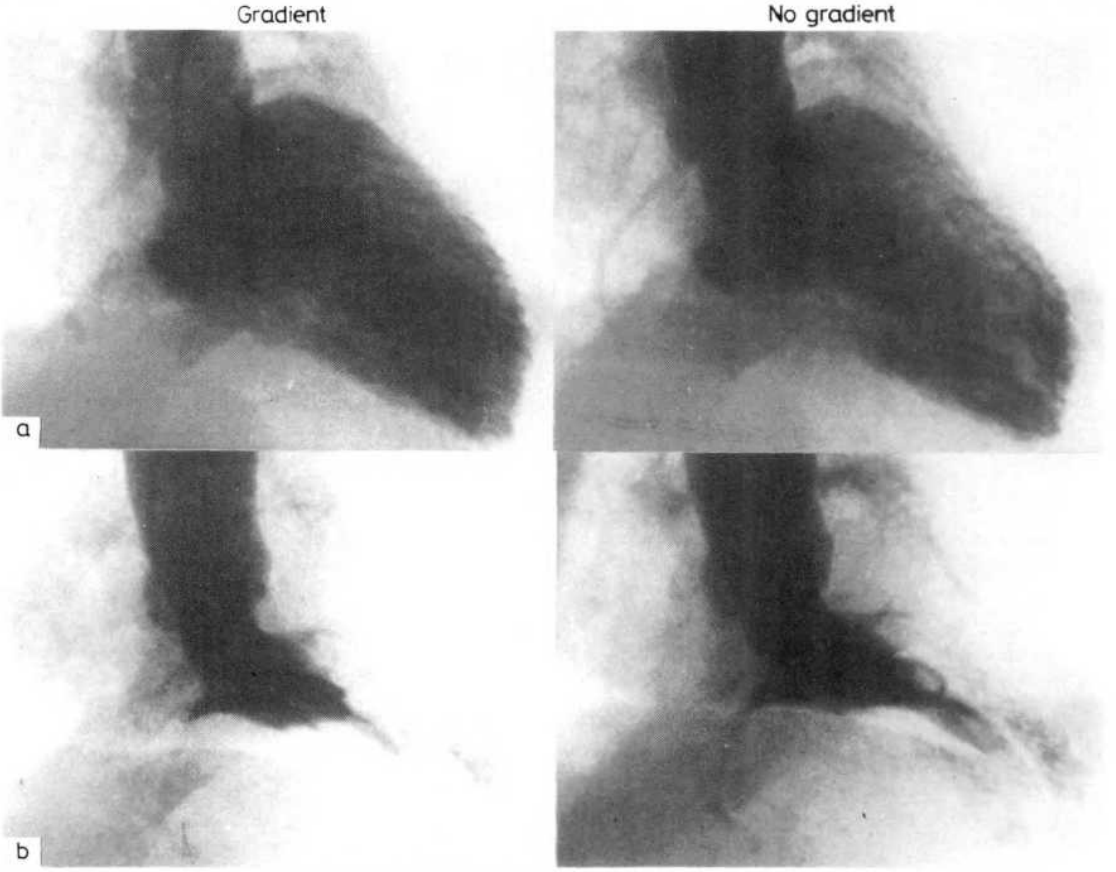

Fig. 5 *Case 2: angiographic frames during (a) end diastole and (b) end systole of the postextrasystolic beat (gradient 110 mm Hg) and of the beat without a gradient. The degree of cavitary obliteration is increased during the postextrasystolic beat.*

A non-obstructive explanation of these unique haemodynamic features of hypertrophic cardiomyopathy has been that the ventricle ejects blood rapidly and obliterates the cavity.[18 19] The data from our patients are consistent with the Gauer phenomenon, in which the pressure gradient results from the progressive separation of the body and outflow tract of the left ventricle. These two regions are not separated by an obstruction but by the opposing walls of the essentially empty body of the ventricle, which contract isometrically once the intracavitary contents have been ejected.[15] Cavity obliteration is therefore the antithesis of obstruction, in that the ventricle is unimpeded in its emptying. The ejection dynamics of hypertrophic cardiomyopathy have been well characterised by the work of Murgo and colleagues, who found a shortened ejection phase measured with a flow-velocity probe in the aortic root in patients with or without pressure gradients.[21] Closure of the aortic valve occurred considerably after the cessation of forward flow, following the onset of ventricular relaxation.[21] Ventricular diastolic function is known to be abnormal in hypertrophic cardiomyopathy, with a delayed relaxation and diminished distensibility,[6 31-33] and the prolonged ejection time may be more related to abnormalities of diastolic relaxation than prolongation of ejection.[34]

"Catheter entrapment"[24] describes artifactually high left ventricular pressures which can be recorded from catheters embedded in the myocardium which measure subendocardial myocardial tissue pressure. Although catheter entrapment has been equated with cavity obliteration,[24] they are quite different phenomena. Unlike catheter entrapment blood is ejected during systole from the open end of a catheter in an obliterating cavity and the pressure decline is not delayed.[15 19] The validity of high inflow tract pressure as a criterion for true obstruction[24] can be questioned when the inflow tract is seen to be obliterated in angiograms (Figs. 3 and 5) and cross sectional

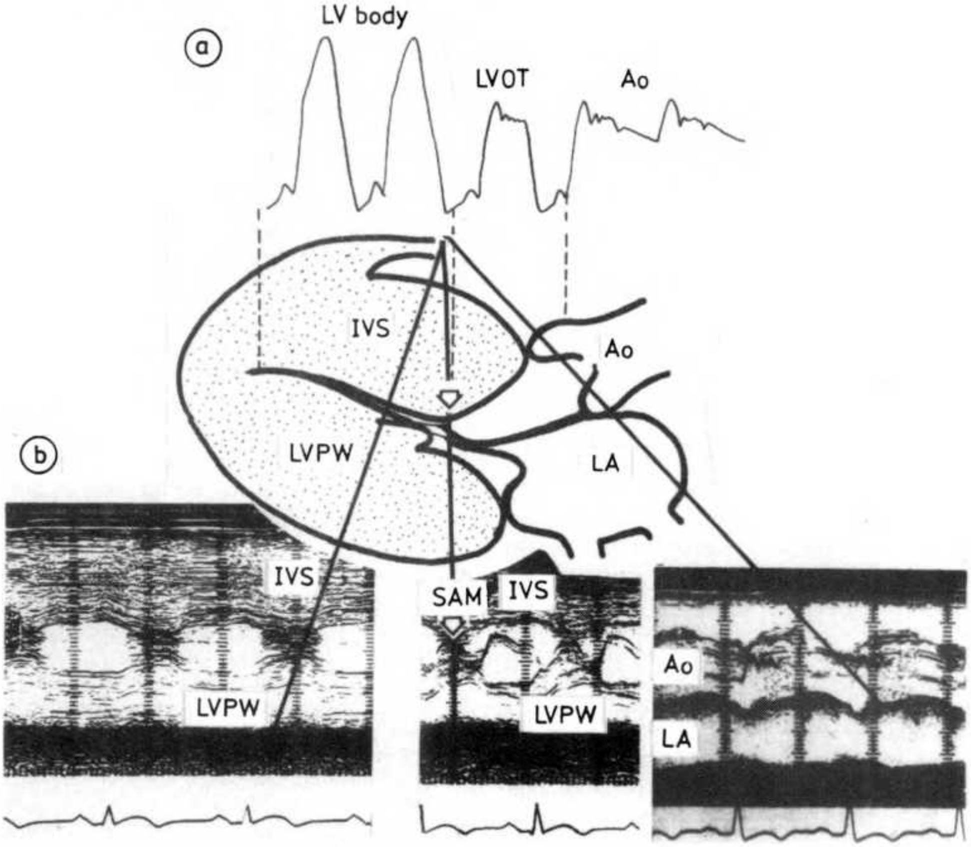

Fig. 6 *(a) Diagram of the relation between the pressure gradient, systolic anterior motion (SAM), and the obliterated left ventricular (LV) cavity based on the parasternal long axis cross sectional echocardiogram of a patient with hypertrophic cardiomyopathy and vertically aligned with a left heart pressure withdrawal recording so that the site of the pressure change can be seen at the junction of the obliterated body of the ventricle and the patent outflow tract (LVOT). The outflow tract is in free communication with the aorta (AO) and shares the same systolic pressure, while the pressure in the body is higher because of the progressive separation of the two left ventricular zones by cavitary obliteration. (b) Three M mode echocardiograms showing systolic anterior motion (centre panel and cross sectional long axis view), which is seen to be a result of the complete emptying of the ventricle. The beam angles are shown. IVS, interventricular septum; LVPW, left ventricular posterior wall; LA, left atrium.*

echocardiograms[35] (Fig. 6).

The increased ejection fractions in patients with hypertrophic cardiomyopathy and the trend toward higher values in hypertrophic cardiomyopathy patients with resting pressure gradients (Fig. 1) has been previously documented using radiographic and radionuclide left ventriculography[31 36] and accords with the concept of an obliterated rather than an obstructed ventricle. When the ejection fraction was compared in the same patient with and without a gradient it did not fall when the gradient was induced as would be expected with the imposition of an obstruction but rose in all instances.

Two different mechanisms were used in altering the gradient in the patients who had comparisons of left ventricular emptying in the current study. It could be argued that the patient with a postextrasystolic pressure gradient (Figs. 4 and 5) was able to overcome the "obstruction" by increasing the left ventricular pressure through the Frank-Starling effect and the increased inotropic state. Nevertheless, the left ventricular pressure and heart rate remained constant when a gradient was induced by the infusion of sodium nitroprusside in another patient (Fig. 3), and the rate and degree of emptying were enhanced in the presence of an 87 mm Hg gradient, which would again belie the imposition of an impediment to ejection.

There are limitations to a contrast angiographic approach to the study of left ventricular emptying in the bizarre, heavily trabeculated ventricles characteristic of hypertrophic cardiomyopathy. Nevertheless, the high ejection fraction, small end systolic cavity size, and more rapid than normal rate of ejection have been repeatedly confirmed by other investigators using radionuclide angiography,[36-38] echocardiography,[35] and four different configurations of flow velocity probes: intraoperative cuff electromagnetic probes,[28] dual lumen catheters,[39] catheter mounted electromagnetic probes,[21] and non-invasive Doppler devices.[40] Thus it is unlikely that the validity of the angiographic data can be discounted.

This study shows rapid complete and apparently unimpeded emptying of the left ventricle despite the presence of a pressure gradient and systolic anterior motion of the mitral valve and suggests an alternative interpretation of the close correlation between the two phenomena[12] which has conventionally been viewed as cause (systolic anterior motion) and effect (gradient). Rapid and complete emptying can apparently be the cause of systolic anterior motion and the gradient, and earlier systolic anterior motion-septal apposition could merely reflect earlier obliteration of the cavity and therefore more time for contractile energy to be expended on isometric contraction (Fig. 6). Systolic anterior motion[41] as well as non-obstructive pressure gradients[16 17] have been found in patients without hypertrophic cardiomyopathy who have hypovolaemic hypercontractile ventricles. We therefore suggest that evidence of hindrance to emptying should be the criterion for the presence of obstruction and not the presence of a pressure gradient or systolic anterior motion in patients with hypertrophic cardiomyopathy.

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Atrial septal aneurysm—a potential cause of systemic embolism

An echocardiographic study

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SUMMARY Atrial septal aneurysm is an uncommon condition. Between 1981 and 1984 10 cases of atrial septal aneurysm were diagnosed by real time cross sectional echocardiography performed in 4840 patients. The aneurysm was associated either with mitral valve prolapse (three patients) or with atrial septal defect (three patients) or occurred in isolation (four patients, two of whom had had a previous embolic event leading to the diagnosis of atrial septal aneurysm by cross sectional echocardiography). During cross sectional echocardiography the aneurysm appeared as a localised bulging of the interatrial septum, which was best seen in the subcostal four chamber view and in the parasternal short axis view at the level of the aortic root. The aneurysm either protruded into only the right atrium (five patients) or moved backwards and forwards between the right and the left atria during the cardiac cycle (five patients). This motion pattern might be related to changes in the interatrial pressure gradient. The two patients who had had a systemic embolism were given anticoagulant treatment, but none underwent surgery.

It is concluded that the true prevalence of atrial septal aneurysm might have been underestimated before the routine use of cross sectional echocardiography, that cross sectional echocardiography enables definitive diagnosis of this condition by a non-invasive technique, and that an atrial septal aneurysm should be suspected and looked for by cross sectional echocardiography after an unexplained systemic embolism.

Atrial septal aneurysm is a localised deformity of the interatrial septum which protrudes into the right or the left atrium or both.[1] It might result from bulging of septum primum tissue through the fossa ovalis.[2] This lesion, which is uncommon, is often unrecognised in asymptomatic subjects.[3 4] Serious complications such as embolic phenomena may, however, occur.[5–9] Cross sectional echocardiography is a non-invasive technique that allows these aneurysms to be diagnosed definitively. With the exception of 11 cases reported by Hauser *et al*,[10] cross sectional echocardiography has been undertaken in only single or a few cases.[3 8 11–19] In our study, 10 cases of atrial septal aneurysm were diagnosed in three years using cross sectional echocardiography. The aneurysm was detected after a systemic embolism in two of the 10 patients. The aims of this study were *(a)* to determine the clinical circumstances leading to the detection of atrial septal aneurysm by cross sectional echocardiography, *(b)* to assess the prevalence of associated cardiac lesions, *(c)* to analyse in detail the echocardiographic patterns of atrial septal aneurysm, and *(d)* to emphasise the need for looking for such aneurysms after unexplained systemic embolism.

Patients and methods

Between March 1981 and January 1984, cross sectional echocardiography was performed in 4840

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Table *Clinical and echocardiographic features in patients with atrial septal aneurysm (ASA)*

Case No	*Sex/age (yr)*	*Reason for cross sectional echocardiography*	*Associated lesions*	*Direction of ASA bulging*
1	M/61	Systemic embolism	None	RA to LA
2	M/43	Systemic embolism	None	RA
3	M/53	Systolic murmur	MVP	RA to LA
4	M/39	Systolic click	MVP	RA to LA
5	F/55	Systolic click and murmur	MVP and TVP	RA
6	F/18	ASD	ASD	RA
7	F/49	ASD	ASD	RA
8	F/74	Suspected mitral stenosis	ASD	RA
9	F/71	Chronic dyspnoea	None (EV)	RA to LA
10	F/70	Suspected pericarditis	None	RA to LA

ASD, atrial septal defect; MVP, mitral valve prolapse; TVP, tricuspid valve prolapse; EV, eustachian valve; RA, right atrium; LA, left atrium.

patients. Of these, 10 (0·2%) were found to have atrial septal aneurysm. Four patients were men and six women (age 18–74 (mean 53) years). Systemic embolism was the reason for cross sectional echocardiography in two of these 10 patients. In the remaining eight cross sectional echocardiography was undertaken because of *(a)* an abnormal systolic mumur or click or both (n=3), *(b)* a known atrial septal defect (n=2), *(c)* suspected mitral stenosis (n=1) or pericardial effusion (n=1), or *(d)* chronic dyspnoea (n=1) (Table).

Cross sectional echocardiography was performed using a mechanical (ATL) or a phased array (Varian 3400, Kontron 250) sector scanner with a 2·25 MHz transducer. Examination was carried out with the patient either semisupine or in the left lateral decubitus position using parasternal, apical, and subcostal views. A simultaneous electrocardiographic lead was recorded. Cross sectional echocardiographic images were recorded on a Panasonic videotape for delayed analysis. M mode echocardiograms were recorded at 50 mm/s using a strip chart recorder. Contrast echocardiography was performed in one patient by rapidly injecting normal saline solution (10 ml) into an antecubital vein.

The diagnostic criterion for atrial septal aneurysm was localised bulging of the interatrial septum, protruding >6 mm into the right or left atrium or both. Bulging of the entire atrial septum or localised bulging protruding <6 mm was not considered to be a true aneurysm. The aneurysmal deformity always affected the middle part of the interatrial septum—that is, the fossa ovalis area—and was seen in the subcostal or apical four chamber views and in the parasternal short axis view at the level of the aortic root. A significant left to right shunt at the atrial level was suspected if the right ventricle was appreciably enlarged (right ventricular end diastolic diameter to left ventricular end diastolic diameter ratio >0·5) with paradoxical motion of the interventricular septum. Mitral or tricuspid valve prolapse or both was diagnosed in the parasternal long axis or apical four chamber view using previously described criteria.[20]

Results

The 10 patients with atrial septal aneurysm were classified into four groups according to their clinical findings.

SYSTEMIC EMBOLISM (GROUP 1)

An atrial septal aneurysm was detected in two patients (cases 1 and 2) by cross sectional echocardiography

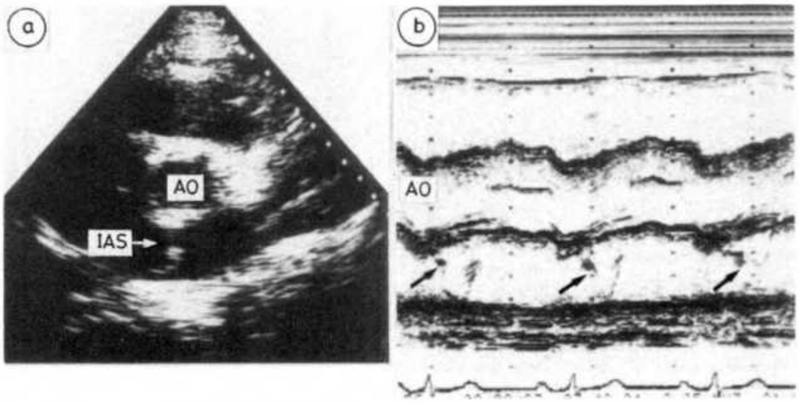

Fig. 1 *(a) Cross sectional echocardiogram in the parasternal short axis view at the aortic root level (case 1) showing the interatrial septum (IAS) bulging into the left atrium (arrow). (b) Simultaneous M mode recording showing an abnormal echo in the left atrium during systole (arrows). AO, aorta.*

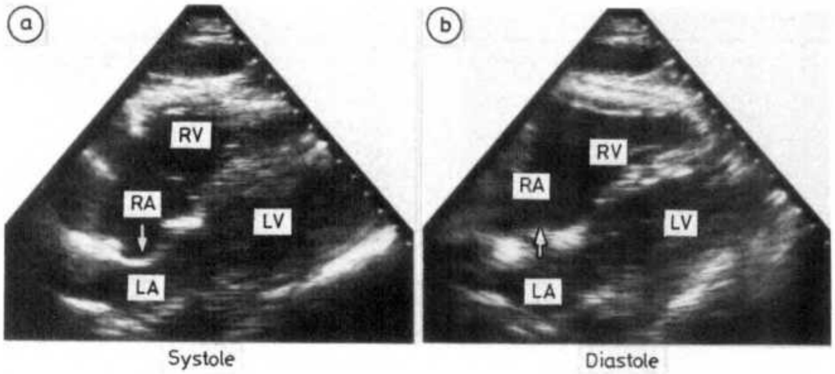

Fig. 2 *Cross sectional echocardiograms in the subcostal four chamber view (case 1) showing the atrial septal aneurysm bulging into (a) the left atrium (LA) during systole (arrow) and (b) the right atrium (RA) during diastole (arrow). LV, left ventricle; RV, right ventricle.*

after a history suggesting arterial embolism.

Case 1—A 61 year old man, who had been previously well, was referred to our institution because of a sudden and permanent right hemiplegia. Physical examination and an electrocardiogram were normal. A computed tomogram of the brain showed a low density area in the left frontoparietal region suggesting an ischaemic cerebral infarct. Embolism was suspected in view of the suddeness of the stroke and because of the absence of hypertension. Intravenous digital subtraction angiography of the cervical vessels was normal as was the 24 hour electrocardiographic recording. An atrial septal aneurysm was detected by cross sectional echocardiography. A parasternal short axis view showed systolic bulging of the interatrial septum into the left atrium. A simultaneous M mode recording showed an abnormal echo in the left atrium moving posteriorly during early systole and anteriorly during mid systole (Fig. 1). A subcostal four chamber view showed a thin outpouching in the middle part of the interatrial septum, bulging into either the left atrium or the right atrium throughout the cardiac cycle (Fig. 2). The motion of the aneurysm was more clearly seen on a simultaneous M mode recording. The aneurysm moved from the right atrium towards the left atrium during mid diastole, end diastole, and early systole. It then suddenly moved in reverse from the left atrium towards the right atrium during mid systole, end systole, and early diastole (Fig. 3). Contrast echocardiography showed a filling defect in the right atrium corresponding to the protrusion of the aneurysm. There was no evidence of contrast shunting. Right heart catheterisation showed normal right sided and pulmonary capillary wedge pressures without any intracardiac shunt. Cineangiography was performed with an injection of contrast into the right atrium. It confirmed the presence of a small atrial septal aneurysm distorting the middle part of the interatrial septum and protruding into the left atrium during atrial early diastole. Anticoagulant treatment was started. The patient had no further emboli during six months' follow up.

Case 2—A 43 year old man was referred after an acute arterial occlusion of the right leg which later resolved. Physical examination and an electrocardiogram were normal. Arteriography showed an abrupt occlusion of both superficial femoral arteries. The popliteal arteries were revascularised through the profunda femoris arteries. A bilateral femoral embolism was then suspected. There was no aortic aneurysm, and a 24 hour electrocardiogram showed no arrhythmia. Cross sectional echocardiography showed an

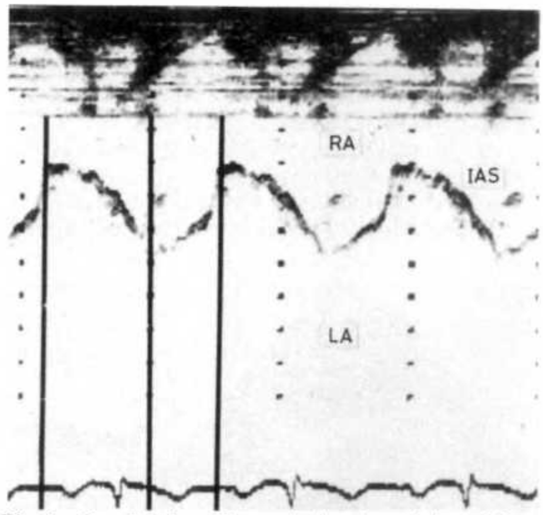

Fig. 3 *M mode echocardiogram in the subcostal view of the aneurysmal motion (case 1) showing the interatrial septum (IAS) moving from the right atrium (RA) towards the left atrium (LA) during mid diastole, end diastole, and early systole and in reverse from the LA towards the RA during mid systole, end systole, and early diastole. Vertical lines emphasize the sudden reversal of the aneurysm from one atria to the other.*

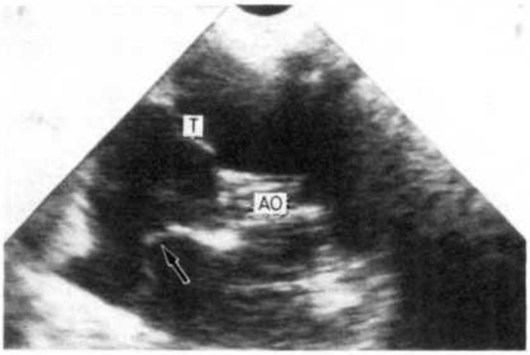

Fig. 4 *Cross sectional echocardiogram in the parasternal short axis view at the aortic root level (case 6) showing the atrial septal aneurysm bulging into the right atrium (arrow). T, tricuspid valve; AO, aorta.*

atrial septal aneurysm bulging into only the right atrium in the apical four chamber view. A right femoropopliteal bypass graft was performed because of persistent rest pain. Anticoagulant treatment was started. No embolic event recurred during four months' follow up.

MITRAL VALVE PROLAPSE (GROUP 2)

Atrial septal aneurysm was detected in association with mitral valve prolapse in two patients (cases 3 and 4) and with tricuspid valve prolapse in one (case 5). In all three cases cross sectional echocardiography was undertaken because of an abnormal systolic murmur or click or both. The atrial septal aneurysm either bulged only into the right atrium (case 5) or undulated alternately between the right atrium and left atrium throughout the cardiac cycle, with the same motion pattern as in case 1 (cases 3 and 4).

ATRIAL SEPTAL DEFECT (GROUP 3)

Atrial septal aneurysm and atrial septal defect were detected in three patients (cases 6, 7, and 8). The aneurysm was associated with a previously known atrial septal defect in two of them (cases 6 and 7). One patient was referred because of suspected mitral stenosis. Cross sectional echocardiography did not confirm the diagnosis but detected atrial septal aneurysm with an associated atrial septal defect. The mean ratio of right to left end diastolic ventricular diameters was 0·86. Interventricular septal motion was always paradoxical. In all three cases the aneurysm bulged only into the right atrium (Fig. 4).

NO SYMPTOMS (GROUP 4)

An atrial septal aneurysm was an unexpected finding in two patients (cases 9 and 10). One patient was referred because of chronic dyspnoea (secondary to carcinomatous lymphangitis) and the second because of suspected pericardial effusion (which was not confirmed by cross sectional echocardiography). No other cardiac disease was found in these patients. A eustachian valve was, however, present in one patient (case 9). The aneurysm undulated between both atria throughout the cardiac cycle in both patients.

Discussion

An atrial septal aneurysm usually involves the region of the fossa ovalis.[1,2] It is a localised bulging of the interatrial septum which protrudes into the right atrium or left atrium or both. Its pathogenesis might be explained by an abnormal structure of the interatrial septum or by a change in the normal interatrial pressure gradient or both.[4] An atrial septal aneurysm is usually considered to be extremely rare. Nevertheless it was detected in 0·2% of 4840 patients in this study and was found at necropsy in 1% of adults by Silver and Dorsey.[2] The true prevalence of atrial septal aneurysm might therefore have been underestimated in the past for two reasons. Firstly, diagnosis may be overlooked because an atrial septal aneurysm often produces no symptoms. Secondly, no non-invasive diagnostic techniques were available before the advent of cross sectional echocardiography. Sixty three cases of atrial septal aneurysm have been found, of which 36 were reported between 1934 and 1979. A diagnosis was made before death in only seven cases using angiocardiography,[4–6,9,21,22] whereas the aneurysm was found at necropsy in the remaining cases.[2,23–29] In contrast, 27 cases were reported between 1978 and 1984 and all were diagnosed before death either by cross sectional echocardiography[1,3,8,10–19] or more recently by intravenous digital subtraction angiography.[7] The frequency of diagnosing atrial septal aneurysm during life seems likely to increase in the next few years with the development of cross sectional echocardiography. This non-invasive technique might become the standard diagnostic procedure, though its sensitivity and specificity have yet to be established. The other diagnostic techniques which have been proposed are M mode echocardiography and angiocardiography. M mode echocardiography can detect abnormal echoes within the right or left atrium, but these findings are neither constant nor specific.[1,15] Angiocardiography is an invasive technique, which does not allow direct visualisation of the interatrial septum. Furthermore, an atrial septal aneurysm may be mistaken for an intra-atrial tumour or thrombus with angiocardiography.[4,9,22] Intravenous digital subtraction angiocardiography, which is not completely invasive, could, however, improve the detection rate.[7]

Atrial septal aneurysm can be diagnosed definitively by cross sectional echocardiography.[1] The localised thin and mobile outpouching of the interatrial septum is best visualised in the subcostal four chamber view and in the parasternal short axis view at the level of the aortic root. A minimum radius of 6 mm for the aneurysm was a diagnostic criterion in this study since a small pocket of 3–6 mm long, extending anteriorly and to the left of the limbus fossae ovalis, has been described anatomically in normal subjects.[30] The mean value for the radius of the atrial septal aneurysm was 10 mm (range 7–15 mm) in this study. In all cases, the atrial septal aneurysm affected the middle part of the interatrial septum—that is, the fossa ovalis area. In some cases the aneurysm seemed to be wider but it never affected the entire atrial septum. Generalised bulging of the interatrial septum was not considered to be a true aneurysm since such bulging might be seen despite the absence of a true aneurysm.[1] Furthermore, an aneurysm affecting the entire atrial septum has never been documented pathologically.[1] Since no patient in this study underwent surgical or postmortem examination, we cannot confirm that the atrial septal aneurysm was strictly confined to the fossa ovalis area or that it was wider.

Whether or not the aneurysm bulges into the right atrium or the left atrium or both depends on the interatrial pressure gradient.[4 11] If the pressure gradient is normal, the aneurysm usually protrudes into the left atrium during early systole and into the right atrium during early diastole as shown in Fig. 3.[11 15] This motion vaguely resembles that of the normal interatrial septum, as described by Tei *et al*[31] Five of the 10 patients in the present study had such a motion pattern (three patients with isolated atrial septal aneurysm and two with associated mitral valve prolapse). The aneurysm may bulge into the left atrium in early systole solely during inspiration.[11] If the interatrial pressure gradient is reversed because of raised pressure in the right atrium, as seen in tricuspid atresia or hypoplastic right heart syndrome, the aneurysm protrudes into the left atrium.[12 13 21] Conversely, if the interatrial pressure gradient is increased because of raised pressure in the left atrium, as seen in mitral stenosis, the aneurysm bulges into only the right atrium.[1 4 22 28] The aneurysm protruded into only the right atrium in five patients in this study, including the three with an associated atrial septal defect, which is in agreement with other reports.[1 3 5 7] In the two other cases (one isolated aneurysm and one aneurysm associated with mitral valve prolapse) the lack of bulging into the left atrium might be explained either by an unknown increase in the left atrial pressure or by an end expiratory cross sectional echocardiogram.[11] Nevertheless, we can only speculate on the relation between the motion pattern of the aneurysm and the interatrial pressure gradient since no patient in this study underwent left heart catheterisation. In addition, cross sectional echocardiography allows detection of a shunt at the atrial level using contrast.[32]

An interesting finding in this study was the detection of atrial septal aneurysm after an unexplained systemic embolic episode in two of the 10 cases. Only six cases of atrial septal aneurysm associated with embolism have been reported to date. Four cases of cerebral embolism with an angiographically documented atrial septal aneurysm have been reported.[5 7 8] Other territories have been reported as the site of an embolism resulting from atrial septal aneurysm including the coronary[6] or pulmonary[9] arteries. We can only speculate on the relation between atrial septal aneurysm and peripheral embolism in this study. Such a relation should be considered likely only if a previously visualised thrombus within the atrial septal aneurysm after a peripheral embolism has disappeared. Hitherto, cross sectional echocardiography has not visualised such a thrombus in any case of atrial septal aneurysm. The embolic potential of atrial septal aneurysm is, however, supported by previous findings: the presence of a thrombus at the base of the aneurysm at necropsy[2] or histological evidence of a partly organised thrombus in a resected atrial septal aneurysm.[5] Another cause of systemic embolism might be paroxysmal arrhythmias, since the triggering role of atrial septal aneurysm in such arrhythmias has recently been suggested.[10] This embolic risk could make what would otherwise have been a simple anatomical anomaly a potentially severe disease. This has led some authors to propose surgical repair of atrial septal aneurysm associated with peripheral embolism in order to prevent the risk of embolic recurrence and to avoid the need for anticoagulant treatment.[5 8] Other complications of atrial septal aneurysm have been reported in association only with large aneurysms. They include pulmonary venous obstruction by an atrial septal aneurysm or prolapse of an atrial septal aneurysm through an atrioventricular orifice.[2 12 29]

In group 2 the atrial septal aneurysm was associated with a mitral valve prolapse. Such an association was found in 30% (3/10) of our patients, whereas it has previously been reported in only two other cases.[3 16] An abnormal systolic mumur or click or both was heard in all the patients in group 2. Alexander *et al* have suggested that a systolic click might be produced by an atrial septal aneurysm. The sudden reversal of the motion of the aneurysmal bulging from the left atrium into the right atrium during mid systole could explain the click.[15] This hypothesis has, however, been questioned by others, who consider that an associated mitral valve prolapse might cause the click.[33] The association of atrial septal aneurysm and mitral valve prolapse suggests that a myxomatous degeneration might be responsible for both abnormalities.[16] A slightly redundant interatrial septum might, with age and even without change in the intra-atrial pressures, become aneurysmal.[2]

In group 3, the atrial septal aneurysm was associated with an atrial septal defect. It is known that an atrial septal aneurysm can contain multiple perforations or fenestrations, resulting in a significant left to right shunting of blood.[1 3 5] Conversely, the spontaneous closure of an atrial septal defect might result in the formation of an atrial septal aneurysm.[14]

In group 4, the asymptomatic atrial septal aneurysm occurred in isolation and was unexpectedly detected by cross sectional echocardiography. A eustachian valve was noted in one patient (case 9). A partial obstruction of the inferior vena cava by such a eustachian valve might result in the blood flow hitting the fossa ovalis area, which might favour the formation of an atrial septal aneurysm.[4] Isolated atrial septal aneurysms have been previously reported.[15] It must be pointed out that the group 1 patients, who had had an embolic episode, also had isolated atrial septal aneurysm. The management of such asymptomatic and fortuitously detected atrial septal aneurysms is therefore debatable. We believe that further studies are necessary to answer this question.

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Echocardiographic features of impaired left ventricular diastolic function in Chagas's heart disease

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SUMMARY To study left ventricular diastolic function in Chagas's disease, simultaneous echocardiograms, phonocardiograms, and apexcardiograms were recorded in 20 asymptomatic patients with positive Chagas's serology and no signs of heart disease (group 1), 12 with Chagas's heart disease and symptoms of ventricular arrhythmia but no heart failure (group 2), 20 normal subjects (group 3), and 12 patients with left ventricular hypertrophy (group 4). The recordings were digitised to determine left ventricular isovolumic relaxation time and the rate and duration of left ventricular cavity dimension increase and wall thinning. In groups 1 and 2 (*a*) aortic valve closure (A_2) and mitral valve opening were significantly delayed relative to minimum dimension and were associated with prolonged isovolumic relaxation, (*b*) left ventricular cavity size was abnormally increased during isovolumic relaxation and abnormally reduced during isovolumic contraction, and (*c*) peak rate of posterior wall thinning and dimension increase were significantly reduced and duration of posterior wall thinning was significantly prolonged; both of these abnormalities occurred at the onset of diastolic filling. These abnormalities were more pronounced in group 2 and were accompanied by an increase in the height of the apexcardiogram "a" wave, an indication of pronounced atrial systole secondary to end diastolic filling impairment due to reduced left ventricular distensibility. Group 4, which had an established pattern of diastolic abnormalities, showed changes similar to those in group 2; however, the delay in aortic valve closure (A_2) and in mitral valve opening and the degree of dimension change were greater in the latter group.

Thus early isovolumic relaxation and left ventricular abnormalities were pronounced in the patients with Chagas's heart disease and may precede systolic compromise, which may become apparent in later stages of the disease. The digitised method is valuable in the early detection of myocardial damage.

There is increasing evidence[1–3] that left ventricular relaxation and filling abnormalities may be an important component of impaired cardiac function, particularly in patients with ischaemic heart disease and ventricular hypertrophy, above all when associated with inco-ordinate left ventricular contraction.[4 5]

In early Chagas's heart disease, angiographic, echocardiographic, and radionuclide studies[6–8] have detected left ventricular abnormalities consisting of kinetic disorders, especially in the apical or apicoposterior areas, similar to those found in ischaemic heart disease. More recently, left ventricular cineangiography of patients with Chagas's heart disease has shown progressive segmental wall abnormalities and decreased left ventricular distensibility associated with the deterioration in clinical status.[9] In our laboratory, using non-invasive methods (phonocardiography) we found prolongation of the rapid relaxation period in patients in the early stages of Chagas's heart disease.[10]

The purpose of this study was to detect abnormalities of left ventricular diastolic function at rest in patients with early Chagas's heart disease and normal systolic time intervals by studying relaxation, left ventricular filling, and posterior wall dynamics using

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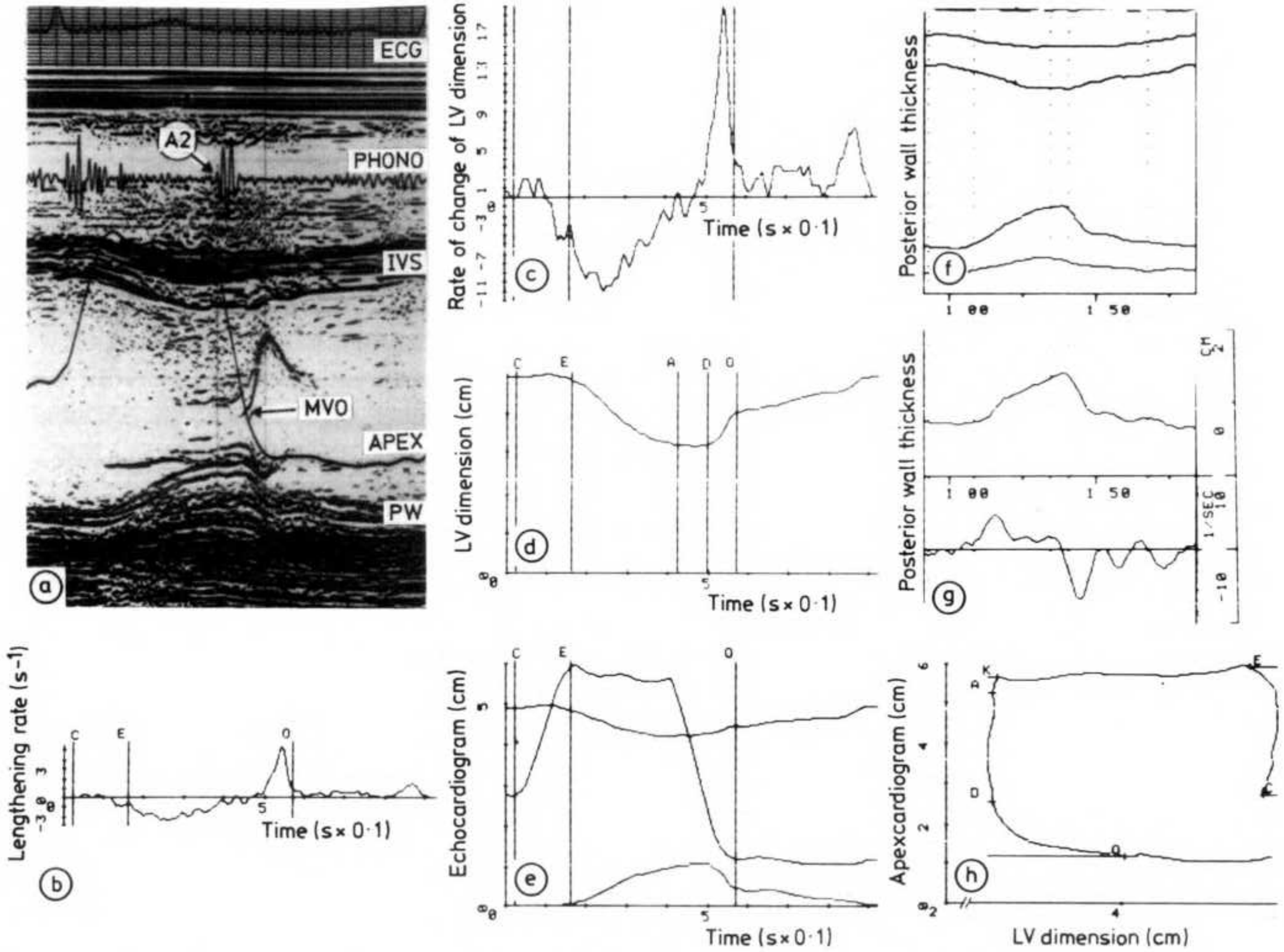

Fig. 1 *(a) Normal left ventricular (LV) M mode echocardiogram and superimposed apexcardiogram (APEX) with simultaneous phonograms (PHONO) (A_2 aortic valve closure) and electrocardiogram (ECG). Computer plots of (b) normalised rate of change of LV dimension (dD/dt × 1/D), (c) rate of change of LV dimension (dD/dt), (d) LV dimension, and (e) the digitised echocardiogram. (f) Normalised rate of change of posterior wall thickness (dPW/dt 1/PW), (g) posterior wall thickness (PW), and (h) the echo dimension apexcardiogram loop—C, E, K, A_2, D (Mo), and O points are indicated (see text). MVO, onset of mitral valve opening; IVS, interventricular septum; PW, posterior wall.*

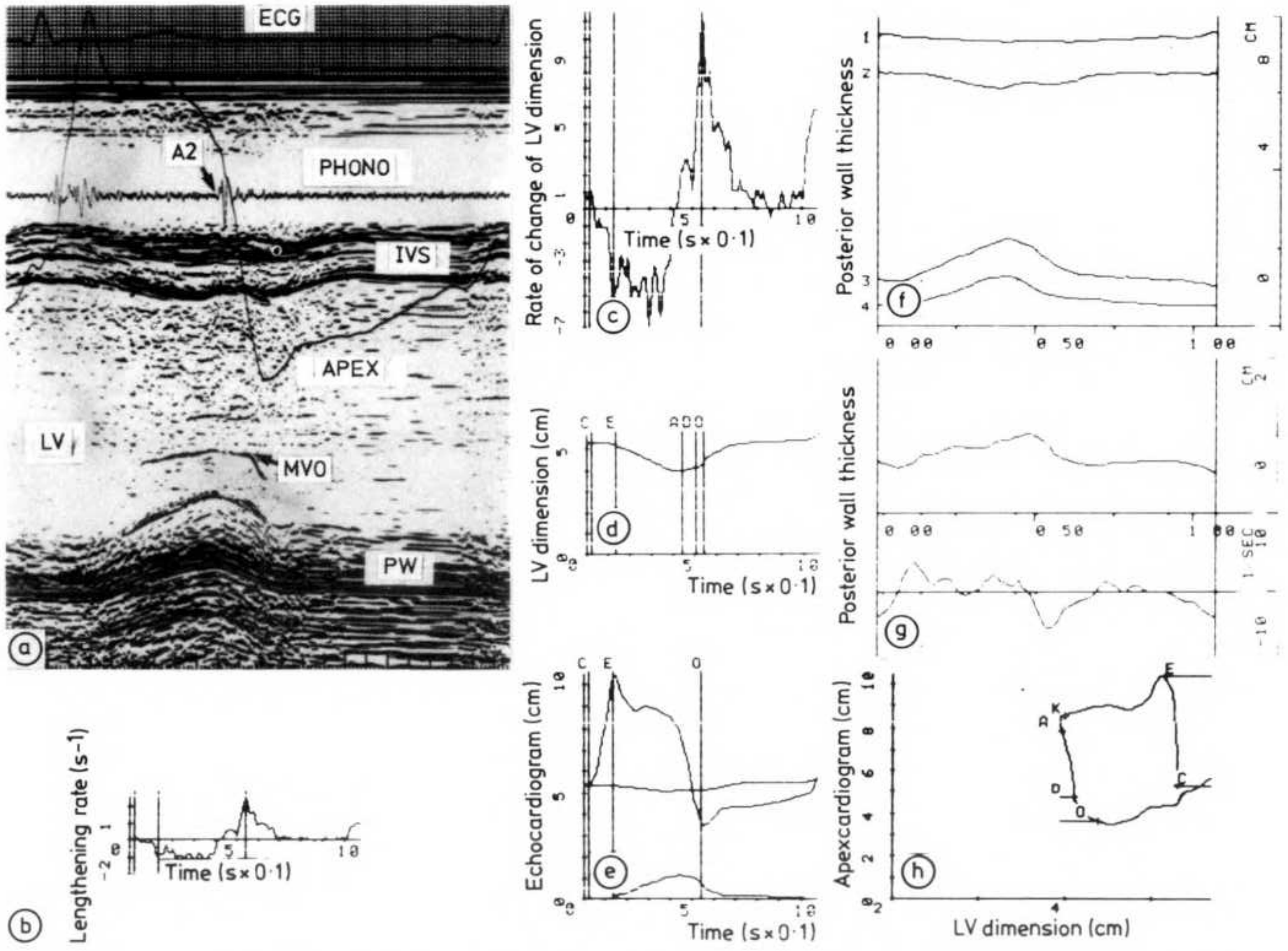

Fig. 2 *M mode echocardiogram and superimposed apexcardiogram from an asymptomatic patient with Chagas's heart disease (group 1). Computer plots as in Fig. 1. There is delayed A_2 and mitral valve opening, and slow and prolonged filling and wall thinning. An abnormal increase in dimension during isovolumic relaxation is seen.*

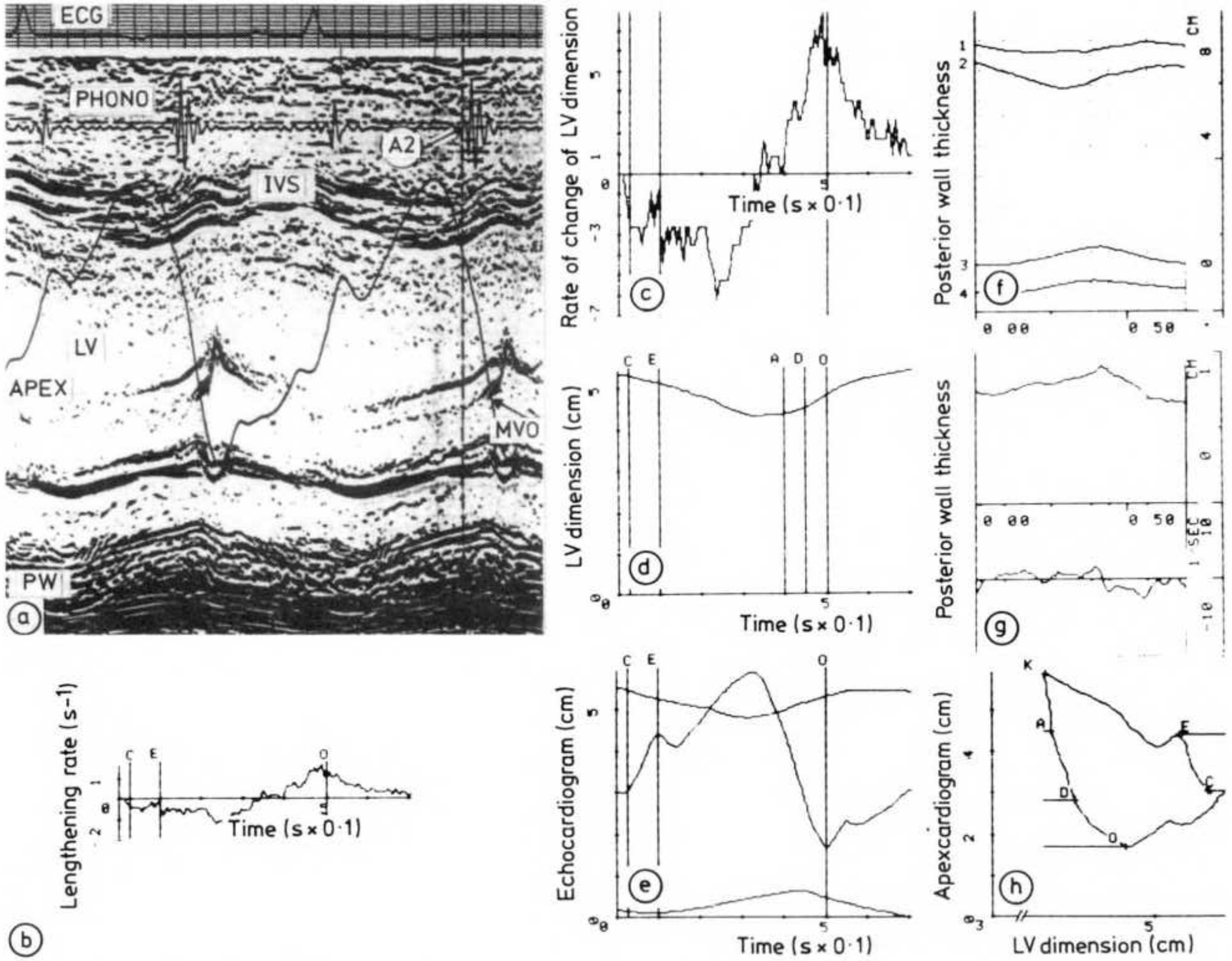

Fig. 3 *M mode echocardiogram and superimposed apexcardiogram from an arrhythmic patient with Chagas's heart disease (group 2). Computer plots as in Fig. 1. The more severe diastolic function abnormalities are later* A_2 *and mitral valve opening and slower and more prolonged posterior wall filling and thinning. There is an abnormal reduction in LV dimension during the upstroke and an increase during the downstroke of the apexcardiogram, both during isovolumic relaxation and before point O (pre-O).*

computerised interpretation of a digitised echocardiogram.

Patients and methods

The study included 50 patients without congestive heart failure or ischaemic heart disease but with serological evidence of past or present *Trypanosoma cruzi* infection, all of whom had a typical history of exposure to infection, came from rural areas where the disease is heavily endemic, and had positive serum complement fixation and indirect haemagglutination tests performed and interpreted according to the Maekelt method.[11] Eighteen subjects were excluded because of technical difficulties in recording the apexcardiogram or echocardiogram or because they had left bundle branch block. Only 32 were suitable for computerised echocardiographic analysis, and they were divided into two study groups (groups 1 and 2). In addition two control groups (groups 3 and 4) were also studied.

Group 1 consisted of 20 (six men, 14 women) asymptomatic subjects with Chagas's disease, most of whom were blood donors detected by the blood bank and referred to us. Their mean (SD) age was 38·8 (9·9) years. All had normal electrocardiograms with only occasional unifocal ventricular extrasystoles, normal chest *x* ray films, and normal M mode and cross sectional echocardiograms.

Group 2 consisted of 12 patients (three men, nine women) with Chagas's disease whose symptoms were directly related to arrhythmias but not to heart failure (New York Association functional class I or II). Their mean age was 45·8 (11·9) years. All had abnormal electrocardiograms consisting of ventricular extrasystoles, most of which were multifocal or in couplets: one had atrial fibrillation and 10 had conduction abnormalities (right bundle branch block (4), left anterior fascicular block (3), isolated left anterior fascicular block (3), abnormal Q waves (3), and nonspecific ventricular repolarisation disorders (10)). All cross sectional echocardiograms showed apical and apicoposterior dyskinesis. These changes were confirmed in seven by left ventricular cineangiograms; all had normal coronary arteriograms.

Group 3—The normal control group consisted of 20 subjects (eight men, 12 women; mean age 30·1 (9·3) years) with no clinical, radiological, or electrocardiographic evidence of heart disease and negative serological tests; all came from urban areas where there were no possibilities of contracting Chagas's infection.

Group 4—The hypertrophic group consisted of 12 patients (six men, six women; mean age 45·1 (14·9) years) of whom six had classic idiopathic hypertrophic cardiomyopathy and six left ventricular hypertrophy secondary to systemic hypertension.

ECHOCARDIOGRAPHY

Echocardiograms with simultaneous apexcardiograms, electrocardiograms (standard lead II), and phonocardiograms (Fig. 1) were performed with the subject in the left lateral position, using a 1·25 cm diameter, 2·25 MHz transducer with a 1000 cycles/second repetition frequency and an Irex echocardiograph. The output was displayed on a strip chart recorder operating at a paper speed of 100 mm/s. A left ventricular echocardiogram of the mitral valve tips clearly showing the onset of opening and providing a clear and constant record of echoes from both the septum and posterior wall endocardium and epicardium was used for further analysis.

The apexcardiograms were recorded using a 3 cm wide microphone air coupled by 25 cm rigid plastic tubing to a transducer, with a time constant of 4 s and a low frequency limit of 0·04 Hz.

The phonocardiograms were recorded with an Irex microphone placed where the high frequency component of the second aortic sound (A_2) could best be recorded.

All recordings were obtained at the end of normal expiration and at least five clear cardiac cycles were recorded. Immediately afterwards, the left ventricular systolic time intervals were measured in the supine position, according to Weissler *et al's* technique.[12]

Digitising techniques

The echocardiograms and apexcardiograms were digitised as previously described by Gibson and Brown.[1] The data processing equipment consisted of an IREX CARDIO 80 microcomputer, a Z80 microprocessor, a graphics/alphanumeric CRT, a digitiser (Summagraphics) 20 × 20 inches with 0·01 inch resolution, and a printer-plotter. A semiautomatic computing system was used.

From the digitised data, plots were made of the left ventricular dimension (D), rate of change of dimension (dD/dt), normalised rate of change of dimension (dD/dt 1/D), normalised rate of change of posterior wall thickness (dPW/dt 1/PW), and of the echo dimension apexcardiogram loops.[4] Figs. 1–3 show examples from subjects in the normal (group 3), asymptomatic (group 1), and arrhythmic (group 2) groups respectively.

Diastolic intervals—Time intervals (ms) were measured *(a)* from the second aortic sound (A_2) to the onset of mitral valve opening (isovolumic relaxation time), *(b)* from minimum left ventricular dimension to A_2, *(c)* from minimum left ventricular dimension to mitral valve opening, and *(d)* between A_2 and the O point on the apexcardiogram (A_2–O). Mean values were obtained for five successive complexes.

Left ventricular dimension changes—Change in left ventricular dimension, expressed as a percentage of

Table 1 *Diastolic time intervals and left ventricular function indices in asymptomatic patients with Chagas's disease (group 1), arrhythmic patients with Chagas's disease (group 2), normal control subjects (group 3), and control subjects with hypertrophy (group 4). Values are mean (1SD)*

Group	*No of patients*	*Diastolic intervals*				*Left ventricular dimension and function*					
		IVRT (ms)	*A_2 to minimum dimension (ms)*	*Minimum dimension to MVO (ms)*	*A_2 to O point (ms)*	*LVEDD (mm)*	*LVESD (mm)*	*FS%*	*PEPc*	*LVETc*	*PEP:LVET ratio*
1	20	72 (14)*	−23 (39)*	48 (39)**	130 (20)	50 (4)	34 (4)*	33 (5)	126 (15)	419 (19)	0·32 (0·06)
2	12	81 (33)	20 (40)***††	102 (50)***††	150 (21)**†	54 (7)*	39 (9)*	29 (9)*	125 (21)	400 (33)	0·34 (0·1)
3	20	63 (11)	−47 (15)	15 (16)	122 (16)	48 (4)	31 (4)	36 (5)	120 (11)	416 (13)	0·30 (0·04)
4	12	81 (25)*	−1 (39)***	80 (33)***	151 (26)**†	43 (6)**†††‡‡	26 (6)**†††‡‡	40 (8)††‡	146 (77)	397 (88)	0·34 (0·11)

Statistical difference from group 3: ***p<0·001; **p<0·01; *p<0·05; from group 1: †††p<0·001; ††p<0·01; †p<0·05; and from group 2: ‡‡p<0·001; ‡p<0·01.
MVO, mitral valve opening; LVEDD, left ventricle end diastolic dimension; LVESD, left ventricle end systolic dimension; FS%, fractional shortening; PEPc, pre-ejection period corrected; LVETc, left ventricular ejection time corrected; PEP:LVET, ratio of pre-ejection period to left ventricle ejection time.

total dimension change during the cardiac cycle, was measured for each of the following intervals: (*a*) isovolumic contraction (between C and E points), (*b*) the apexcardiogram downstroke (between minimum dimension and the O point, pre-O), (*c*) the isovolumic relaxation time, (*d*) and atrial systole (between the beginning of the electrocardiogram P wave and the beginning of the Q wave at the end of the cycle).

The "a":H ratio of the apexcardiogram, which represents the relative magnitudes of the "a" wave in relation to the total outward movement and the "a":D ratio taken as the ratio between the "a" wave height and total diastolic deflection (D).[13]

Left ventricular cavity dynamics—(*a*) Left ventricular end diastolic dimension (LVEDD) was measured at the beginning of the Q wave; (*b*) left ventricular end systolic dimension (LVESD) was taken as the minimum systolic dimension; (*c*) fractional shortening (%FS) was calculated by substracting the end systolic dimension (LVESD) from the end diastolic dimension (LVEDD), and expressing it as a percentage of the LVEDD (LVEDD-LVESD/LVEDD×100%); (*d*) peak rate of increase in left ventricular dimension was calculated as the highest positive value of the dimension change curve in diastole; and (*e*) rapid filling period was arbitrarily defined as the interval between the minimum dimension and reduction to 20% of the peak rate of dimensional increase.[1]

Left ventricular posterior wall dynamics—(*a*) normalised peak rate of posterior wall thinning was taken as the lowest negative value of the mean curve of change in posterior wall thickness during diastole; and (*b*) duration of early thinning of the posterior wall was taken as the interval between maximum posterior wall thickness and the peak rate of posterior wall thinning.

VALIDITY AND REPRODUCIBILITY OF METHODS

Validation of echocardiographic measurements of the left ventricular minor axis and its rate of change has been established by comparison with angiographic data from previous studies.[14 15]

Reproducibility was assessed as the root mean square difference between pairs of determination of left ventricular dimension at end systole and end diastole and of peak rate of increase in left ventricular dimension during filling. These calculations were performed for 20 pairs of measurements made by two observers on the same recording and also in 10 patients between pairs of recordings made at different times in the same patient. For duplicate determinations on the same recording the mean square difference was 1·7 mm for end systole and 1·8 mm for end

Table 2 *Left ventricular (LV) percentage dimensional changes, left ventricular (LV) cavity dynamics, and "a" wave (apexcardiogram) in asymptomatic patients with Chagas's disease (group 1), arrhythmic patients with Chagas's disease (group 2), normal control subjects (group 3), and control subjects with hypertrophy (group 4). Values are mean (1SD)*

Group	*LV dimension change*				*LV cavity dynamics*		*"a" wave*	
	CE (%)	*PRE-O (%)*	*IVR (%)*	*Atrial systole (%)*	*Peak rate of dimension increase (cm/s)*	*Rapid filling period (ms)*	*"a":H (%)*	*"a":D (%)*
1	8·8 (8·4)	37·2 (10·6)	6·9 (6·0)***	21·2 (9·3)*	12·0 (3·1)***	177·1 (72·2)**	9·1 (5·4)	29·5 (13·0)
2	15·6 (12·4)*	48·8 (9·7)***††	19·5 (18·0)**†	17·6 (9·4)	10·1 (3·4)***	225·1 (69·1)***	19·1 (11·3)**†	51·5 (15·8)***†††
3	6·9 (8·9)	34·3 (10·1)	1·5 (2·1)	15·8 (6·2)	16·0 (3·0)	125·7 (29·2)	7·5 (3·5)	23·6 (9·3)
4	23·0 (22·7)*†	41·5 (16·8)	14·4 (9·1)***†	23·8 (13·2)	10·9 (3·7)***	176·9 (63·1)*	19·9 (9·4)***†††	44·7 (13·5)***††

Statistical difference from group 3: ***p<0·001; **p<0·01; *p<0·05; and from group 1: †††p<0·001; ††p<0·01; †p<0·05.
"a":H, ratio of "a" wave to total apexcardiogram height; "a":D, ratio of ""a" wave to total diastolic deflection of apexcardiogram; CE%, change in LV dimension between C and E points of apexcardiogram (expressed as percentage of total dimension change); IVR, isovolumic relaxation time.

Table 3 *Posterior wall (PW) dynamics in asymptomatic patients with Chagas's disease (group 1), arrhythmic patients with Chagas's disease (group 2), normal control subjects (group 3), and control subjects with hypertrophy (group 4). Values are mean (1SD)*

Group	*PW thickness diastole (mm)*	*Peak rate of (N) PW thinning* (s^{-1})	*Duration of PW thinning (ms)*
1	7·5 (1·6)	5·1 (1·9)**	84·3 (46·4)*
2	7·4 (1·5)	3·5 (1·9)***†	114·1 (40·4)***
3	6·9 (1·4)	6·7 (1·8)	59·1 (17·1)
4	12·3 (3·5)***†††‡‡‡	3·6 (1·7)***†	86·2 (54·5)

Statistical difference from group 3: ***$p<0\cdot001$; **$p<0\cdot01$; *$p<0\cdot05$; from group 1: †††$p<0\cdot001$; †$p<0\cdot05$; and from group 2: ‡‡‡$p<0\cdot001$.
N, normalised (dPW/dt 1/PW).

diastole difference and 1·6 cm/s for peak rate of increase of left ventricular dimension.

STATISTICAL METHOD

Normal values were considered to be those found between two standard deviations of the mean values in the normal group. The statistical analysis of the differences between means was determined by Student's *t* test.

Results

Tables 1–3 and Figs. 4–8 show the results (mean (SD)) in the asymptomatic study group (group 1), the study group with arrhythmias (group 2), the normal control group (group 3), and the hypertrophic control group (group 4). Group 3 had diastolic intervals and changes in left ventricular dimension, left ventricular cavity size, and posterior wall dynamics similar to those reported by others.[3 16]

GROUP 1

Although the left ventricular end diastolic dimension, the end diastolic thickness of the posterior wall, the percentage fractional shortening, and the systolic time intervals were normal with respect to the control group, the following significant abnormalities were found (Tables 1–3):

Diastolic intervals—Isovolumic relaxation time was prolonged ($p<0\cdot05$) and mitral valve opening and aortic valve closure were delayed in relation to minimum dimension ($p<0\cdot01$ and $p<0\cdot05$ respectively) (Figs. 4 and 5).

Changes in left ventricular dimension—There was a significant abnormal increase in left ventricular dimension during isovolumic relaxation time ($p<0\cdot001$). Increased change in dimension was found during atrial systole ($p<0\cdot05$) (Fig. 6). As regards the "a":H and "a":D ratios in the apexcardiogram, although there was no significant change, values 2 standard deviations above the mean for the normal

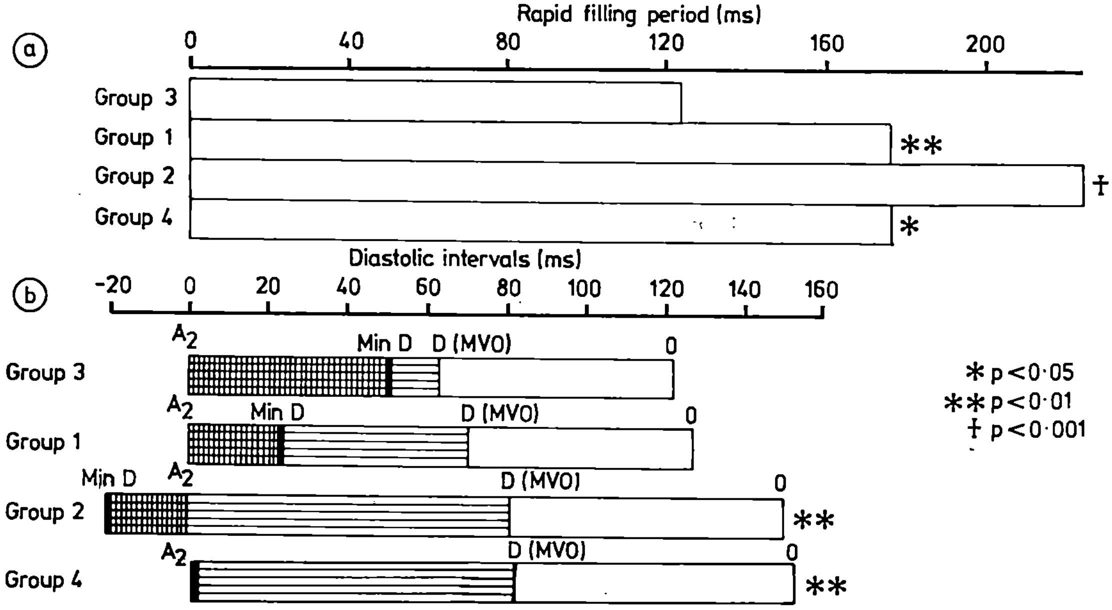

Fig. 4 *(a) Duration of rapid filling period and (b) diastolic intervals in the four groups studied. The significantly prolonged rapid filling time of the asymptomatic and arrhythmic patients with Chagas's disease (groups 1 and 2) and the control group with hypertrophy (group 4) compared with the normal control group (group 3) may be readily seen as well as the progressively delayed* A_2 *mitral valve opening (MVO) and prolonged isovolumic relaxation and* A_2O *intervals.*

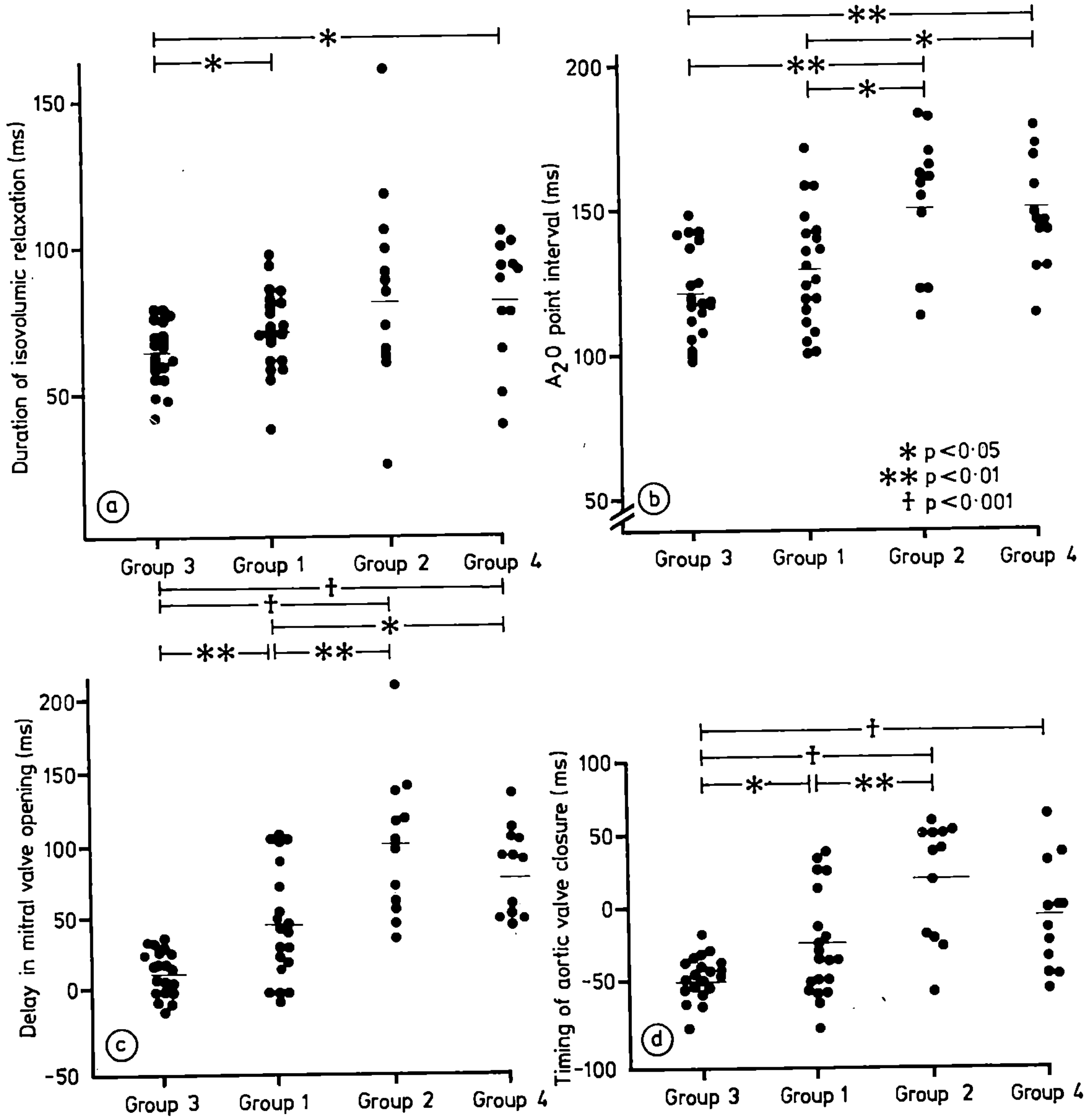

Fig. 5 *(a) Duration of isovolumic relaxation, (b) duration of A_2O point interval, (c) timing of mitral valve opening, (d) timing of aortic valve closure with respect to minimal dimension in normal control subjects (group 3), asymptomatic and arrhythmic Chagas's heart disease patients (groups 1 and 2), and hypertrophic control subjects (group 4).*

group were found in seven out of 20 patients.

Left ventricular cavity dynamics—Left ventricular end systolic dimension was significantly increased ($p<0·05$), the peak rate of increase in dimension was reduced ($p<0·001$), and the duration of the rapid filling period was significantly prolonged ($p<0·01$) (Figs. 7 and 8).

Left ventricular posterior wall dynamics—The normalised peak rate of posterior wall thinning was reduced ($p<0·01$) and early thinning of the posterior wall was prolonged ($p<0·05$) (Figs. 7 and 8).

GROUP 2

This group had a slight increase in both the left ventricular end diastolic dimension and left ventricular

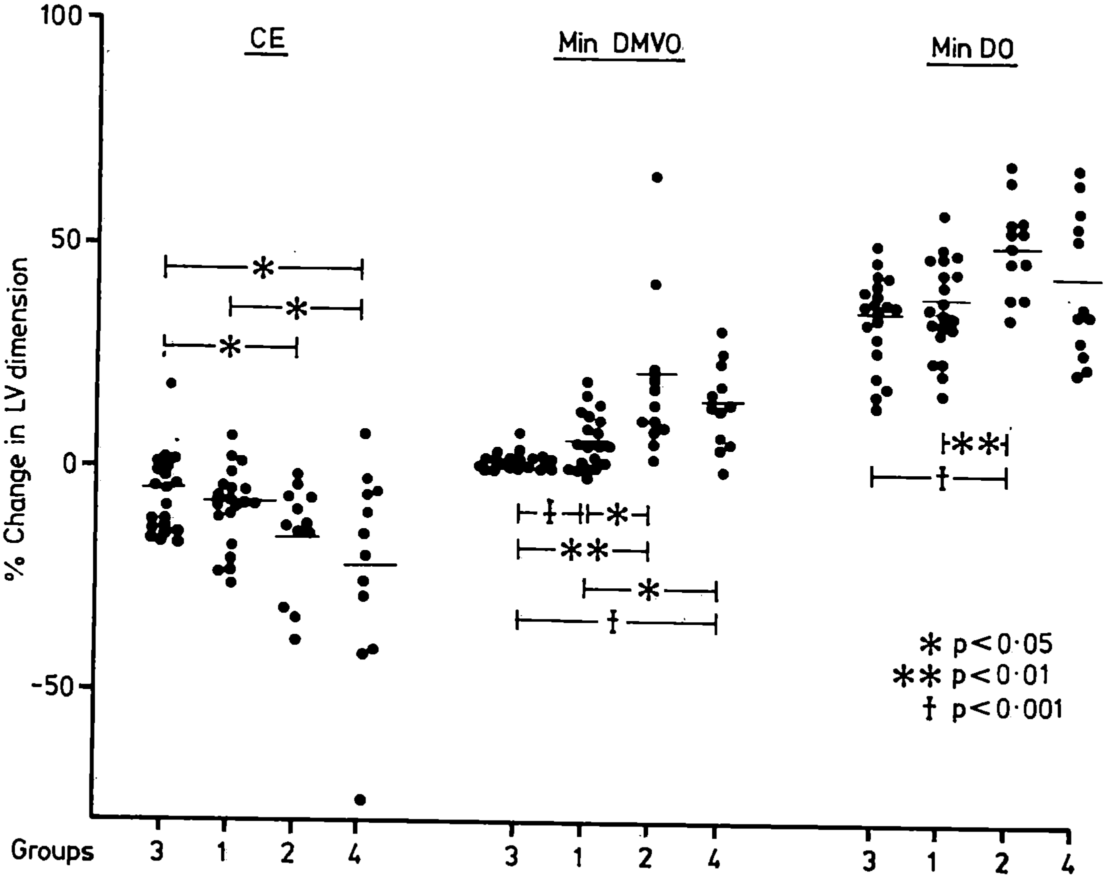

Fig. 6 *Change in LV dimension (expressed as percentage of total dimension change) between C point (apexcardiogram) and E point (CE) and between minimum dimension and mitral valve opening (min DMVO) and between minimum dimension and O point (pre-O) (min DO) in normal control subjects (group 3), asymptomatic and arrhythmic Chagas's heart disease patients (groups 1 and 2), and hypertrophic control subjects (group 4).*

end systolic dimension (53·8 (6·6) mm and 38·6 (8·9) mm) and a slight decrease in fractional shortening (29 (9)%); nevertheless, systolic time intervals and posterior wall thickness remained normal.

The abnormal values for all indices of diastolic function seen in group 1 were of a greater magnitude in group 2 who also had *(a)* increased duration of the A_2–O interval ($p<0{\cdot}01$ and $p<0{\cdot}05$ *vs* groups 3 and 1), *(b)* abnormal reduction in left ventricular dimension during the apexcardiogram upstroke ($p<0{\cdot}05$ *vs* group 3) as well as an abnormal increase during the apexcardiogram downstroke during isovolumic relaxation time ($p<0{\cdot}01$ and $p<0{\cdot}05$ *vs* groups 1 and 3) and before the O point (pre-O) ($p<0{\cdot}001$ and $p<0{\cdot}01$ *vs* group 1 and 3), and *(c)* an increase in the "a":H ratio ($p<0{\cdot}01$ and $p<0{\cdot}05$ *vs* groups 1 and 3) and "a":D ratio in the apexcardiogram ($p<0{\cdot}001$ *vs* groups 1 and 3) (Tables 1–3, Figs. 4–8).

GROUP 4

Left ventricular end diastolic and left ventricular end systolic dimensions were reduced ($p<0{\cdot}01$ *vs* group 3 and $p<0{\cdot}001$ *vs* groups 1 and 2). The fractional shortening and the systolic intervals were normal. End diastolic thickness of the left ventricular posterior wall was increased ($p<0{\cdot}001$ *vs* groups 1, 2, and 3). Diastolic function abnormalities similar to those in group 2 were found; there was, however, less delay in aortic valve closure and mitral valve opening. The increase in dimension during the apexcardiogram downstroke was not significant and the rapid filling period was less prolonged (Tables 1–3, and Figs. 4–8).

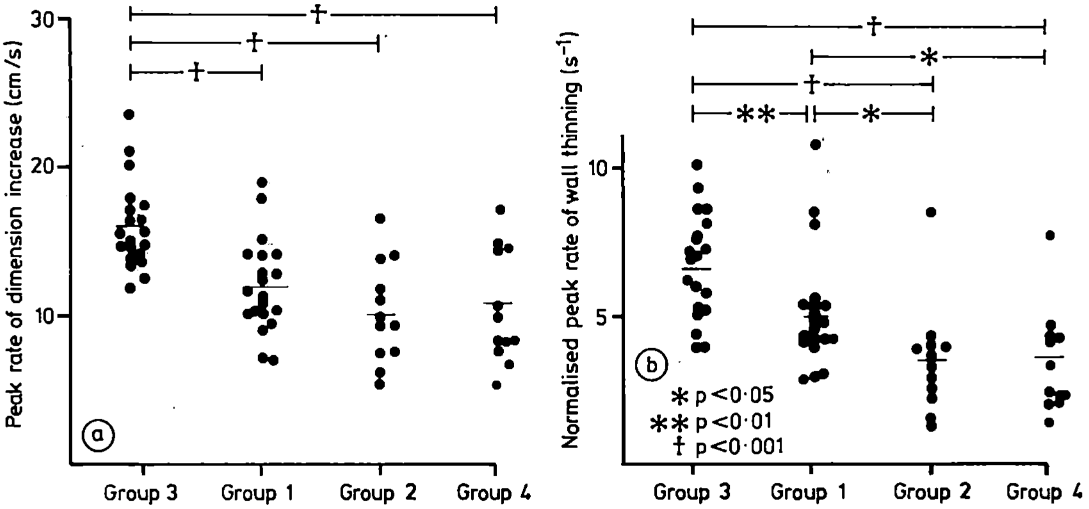

Fig. 7 *(a) Peak rate of increase in left ventricular (LV) dimension in diastole and (b) normalised peak rate of wall thinning in normal control subjects (group 3), asymptomatic and arrhythmic Chagas's heart disease patients (groups 1 and 2), and hypertrophic control subjects (group 4).*

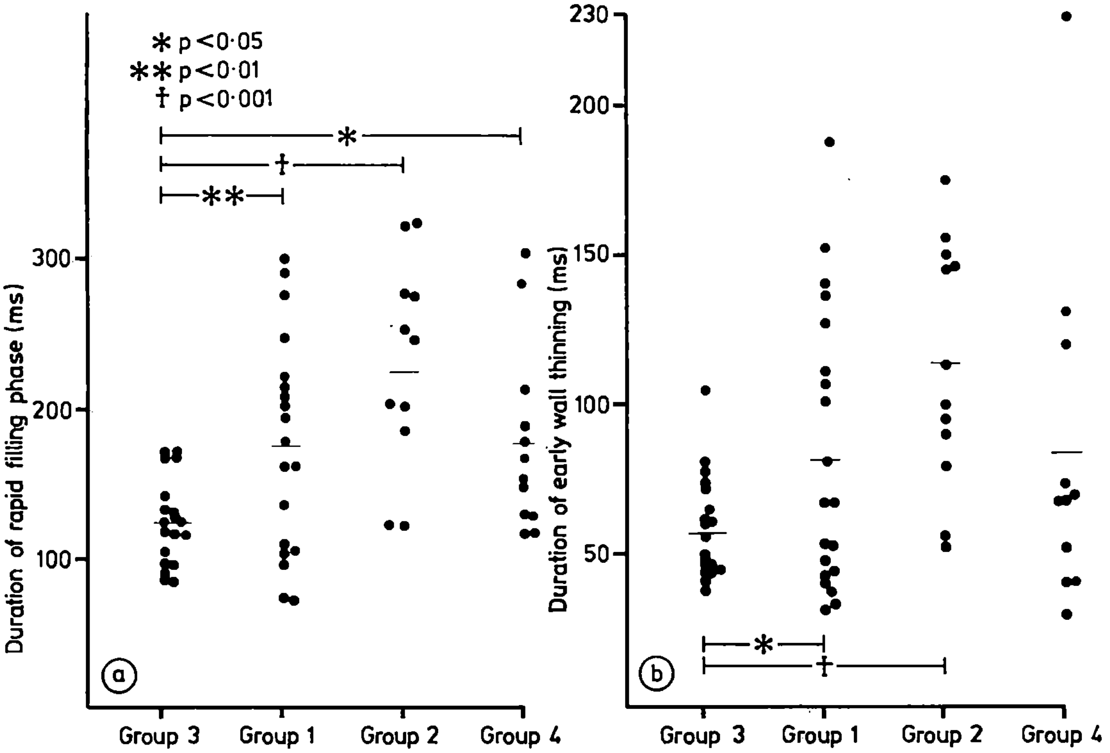

Fig. 8 *(a) Duration of rapid filling and (b) duration of early wall thinning in normal control subjects (group 3), asymptomatic and arrhythmic Chagas's heart disease patients (groups 1 and 2), and hypertrophic control subjects (group 4).*

Discussion

Computerised echocardiographic interpretation is an excellent tool for studying left ventricular diastolic function because it provides not only a continuous record of changes in dimension, wall thickness, and instantaneous dynamics but also allows us to pinpoint the moment mitral valve opening begins and thus to study left ventricular relaxation and filling. It has been useful as a non-invasive method of studying early changes in ventricular function in subjects with ischaemic and valvar heart disease and hypertrophic cardiomyopathy and could be used in the study of other heart diseases.[4] We found it especially useful in patients with early Chagas's heart disease for studying inco-ordinate contraction, which has previously been reported by our group and others.[6–9 17]

Interestingly, important diastolic function abnormalities were found even in the asymptomatic patients with Chagas's disease (group 1) in whom clinical examination, electrocardiograms, chest *x* ray films, and M mode and cross sectional echocardiograms had failed to show any signs of heart disease. The abnormalities were less severe in this group than in those with arrhythmias (group 2).

Firstly, the abnormal diastolic intervals included delayed closure of the aortic valve, delayed mitral valve opening, and prolonged isovolumic relaxation. The delay in aortic valve closure is explained by inco-ordination due to segmental contractility disorders as there are areas of myocardium with delayed or abnormal movements which provoke persistent tension, thus prolonging and delaying the end of ejection.[3] Delayed mitral valve opening would thus be explained not only by the delayed aortic valve closure but by the prolonged isovolumic relaxation time itself.

Secondly, the abnormal changes in left ventricular dimension during the apexcardiogram upstroke (isovolumic contraction), the downstroke (early relaxation), or both consisted of a significant reduction in dimension during the former and an abnormal increase during the latter; when both abnormalities were present, reduction during isovolumic contraction was always accompanied by increase during relaxation. These abnormal dimensional changes were the result of disturbances of function. A decrease in dimension during isovolumic contraction could reflect assynchronous onset of contraction, with areas of myocardium developing early tension and contraction, whereas an increase in dimension during relaxation would reflect increased outward movement of the posterior wall before mitral valve opening occurs, accompanied by a change in isovolumic shape. A similar explanation has been suggested for ischaemic patients with inco-ordinate contraction[4]; however, invasive studies would be needed for confirmation.

Thirdly, the abnormal left ventricular cavity and posterior wall dynamics included prolonged duration of rapid filling and reduced dimensional increase peak rate accompanied by prolonged and reduced posterior wall thinning. This tendency towards early involvement of the posterior wall or apical region in Chagas's heart disease or both had already been confirmed by cineventriculograms, M mode and cross sectional echocardiograms, and radionuclide studies[6–8] and represents the pathological substratum of posterior wall thinning or aneurysms.[18]

In the patients with arrhythmias who already showed signs of heart disease, but without congestive heart failure, the abnormalities of diastolic function were more severe and widespread. Significant differences in relation to the abnormal changes in the asymptomatic group were observed and were also accompanied by other changes, both in early and end diastole. The former consisted of a significant lengthening of the A_2–O interval accompanied by an abnormal increase in the left ventricular dimension before the O point (increased pre-O dimension) and the latter consisting of an increase in the apexcardiogram "a" wave. The first changes would be secondary to a greater abnormality in the velocity and duration of rapid filling[19] and the second would be a sign of a significant atrial systole, during which the left ventricular dimensional change was relatively small and reflected greater resistance to filling during end diastole. Both changes indicate myocardial restriction due to reduced distensibility in Chagas's disease. A good correlation has been reported between increases in the "a" wave, both the "a":H and the "a":D ratios, with diastolic compliance or distensibility, determined by invasive methods in subjects with dilated cardiomyopathy.[13] These abnormal findings in the group with arrhythmias were similar to those in the control group with left ventricular hypertrophy having a known pattern of diastolic abnormalities.[20–23]

Similar changes have also recently been described in subjects with aortic valve stenosis and severe diabetes.[22 24] Although these findings are not specific to Chagas's disease, there are certain differentiating characteristics. The degree of assynchronism (delayed aortic valve closure and delayed mitral valve opening) is greater in patients with Chagas's disease, and the degree of the dimensional changes during the isovolumic periods (both contraction and relaxation) is greater than in subjects with hypertrophy. Moreover, although there is some similarity in patients with ischaemic heart disease as far as the degree of assynchronism and dimensional changes are concerned,[25] in Chagas's disease the isovolumic relaxation period is prolonged and the filling abnormalities are more severe. It is important to point out that a diagnosis of coronary disease can be excluded as a cause in this series because of the absence of symptoms, mean age <43 years, normal coronary angiograms in seven out of 12 (58%) patients in the arrhythmic group, and positive serology for Chagas's disease in 100% of the patients.

Abnormalities in diastolic function have been ascribed to altered myocardial properties (ischaemic disease, hypertrophy)[20 21 26 27] or to microvascular involvement (diabetes).[24]

In Chagas's disease these abnormalities are due to oedema, inflammatory cell infiltration, and destruction of the myocardial fibres. In the more advanced stages, fibrous replacement of myocardial fibres might be a cause contributing to myocardial rigidity.

These findings lead us to believe that the initial manifestation of Chagas's disease is predominantly a diastolic rather than a systolic dysfunction and that only years later the symptoms secondary to severe impairment of pumping or systolic function prevail.

It is a well known fact that in Chagas's disease the initial infection, easily detected by serological tests, is often followed by a latent period which lasts for years or even decades. It is important during this period to detect any sign of heart disease. This not only permits timely therapeutic measures to be taken, such as parasiticide drugs, but also a better assessment of these measures and further knowledge as far as prognosis and the evolution of this disease is concerned.

To our knowledge there is no report of studies of diastolic function in Chagas's disease using non-invasive techniques. Carrasco *et al* found abnormal and progressive changes in left ventricular systolic function and distensibility using invasive studies.[9]

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Vegetations in infective endocarditis
Clinical relevance and diagnosis by cross sectional echocardiography

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SUMMARY Cross sectional echocardiography identified vegetations in 45 of 62 (73%) patients who had clinical evidence of active infective endocarditis. The sensitivity of this technique in diagnosing vegetations in infective endocarditis was 93% and the specificity 89%. The predictive value of a positive test was 96% and that of a negative test 80%. Vegetations were detected with a similar frequency on the aortic and mitral valves. The incidence of valvar incompetence, congestive heart failure, and the need for surgical intervention was similar in the patients with and without vegetations. Embolism occurred in 47% of those patients with vegetations and in 12% of those without. The mortality rate was 27% in those with vegetations, and no patient without vegetations died.

Thus cross sectional echocardiography is accurate in diagnosing vegetations in patients with infective endocarditis, and this finding identifies patients at high risk of embolic complications and death.

Some patients with infective endocarditis have vegetations which may be identified by echocardiography, and this finding has been suggested to indicate a poor prognosis with a high incidence of complications.[1–3] Initial studies were, however, performed using M mode echocardiography,[1–3] and this is less sensitive than cross sectional echocardiography in detecting smaller or anatomically less accessible vegetations.[4–6] Few studies have been carried out that reassess the clinical significance of vegetations detected by wide angle cross sectional echocardiography,[2 5 7] and the surgical implications of this finding therefore remain controversial. The reliability of detecting vegetations by cross sectional echocardiography also requires careful assessment, as the differentiation of vegetations from other valvar abnormalities by M mode echocardiography is difficult.[8] In this study we attempted to solve these problems firstly by reviewing our experience of the accuracy of diagnosis of vegetations by cross sectional echocardiography, and, secondly, by determining the relation between the presence of vegetations and the occurrence of clinical complications in patients with active infective endocarditis.

Patients and methods

Sixty two consecutive patients (42 male, 20 female; mean age 43·8 (range 3–81) years) with the clinical evidence of infective endocarditis underwent cross sectional and M mode echocardiography between December 1979 and May 1983. Follow up was for a mean of 17 (range 1–42) months. All patients had strong clinical evidence of active endocarditis, including two or more of the following features: fever, sweating, heart murmur, splenomegaly, peripheral features of endocarditis, and positive blood cultures. All echocardiographic studies were performed in the standard views during the period of diagnosis and treatment in hospital using a Varian V-3000 (Varian Associates) phased array ultrasonograph. Vegetations were defined as masses, sessile or pedunculated, attached to the cardiac valves or endocardial surfaces.[9]

The clinical records and echocardiographs were reviewed retrospectively and the accuracy of the diag-

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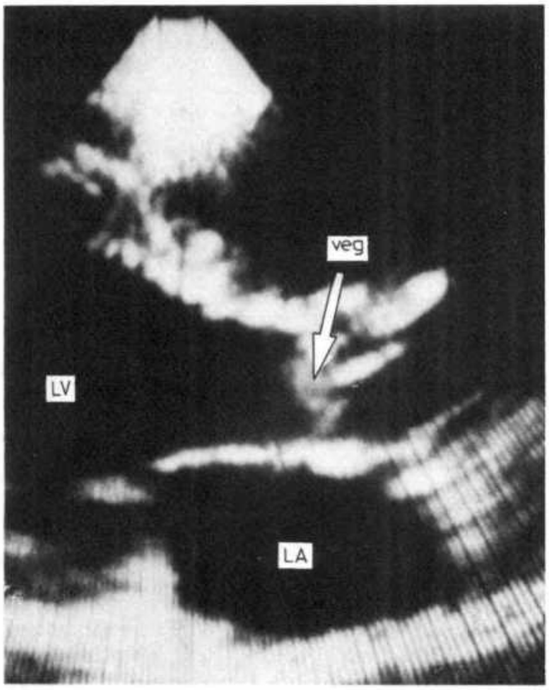

Figure *Cross sectional echocardiogram in the parasternal long axis view showing large vegetations (arrow) attached to the aortic valve leaflets. Veg, vegetations; LV, left ventricle; LA, left atrium.*

Table 1 *Site affected by infective endocarditis in 62 patients with and without vegetations*

Site	*With vegetations* *(n=45)*	*Without vegetations* *(n=17)*
Aortic valve	21	11
Mitral valve	20	5
Tricuspid valve	2	0
Pulmonary valve	0	1
Ventricular septal defect	2	0

Table 2 *Underlying pathology predisposing to infective endocarditis. Figures are numbers of patients*

Pathology	*With vegetations (n=45)*	*Without vegetations (n=17)*
Mitral valve prolapse	9	3
Bicuspid aortic valve	8	3
Rheumatic aortic valve disease	2	1
Rheumatic mitral valve disease	2	1
Mitral valve disease (other)	3	0
Calcific aortic stenosis	2	3
Aortic valve replacement	1	4
Mitral valve replacement	2	1
Ventricular septal defect	2	0
Congenital subvalvar aortic stenosis	1	0
Congenital pulmonary stenosis	0	1
No underlying pathology	13	0

nosis of vegetations by echocardiography assessed by comparing the echocardiographic interpretation with subsequent surgical and necropsy reports of the valvar pathology. The sensitivity, specificity, and diagnostic accuracy of cross sectional echocardiography in detecting vegetations in patients with endocarditis were calculated by the following formulae[10]: sensitivity=TP/(TP+FN), specificity=TN/(TP+FP), diagnostic accuracy of a positive test=TP/(TP+FP), and the diagnostic accuracy of a negative test=TN/(TN+FN), where TP is a true positive, TN a true negative, FP a false positive, and FN a false negative test.

The subsequent clinical course and occurrence of complications were also noted and compared with the echocardiographic features. The results were analysed using Fisher's exact probability test for statistical significance.

Results

Of the 62 patients with active endocarditis, 45 (73%) had vegetations identified by cross sectional echocardiography (Figure), and 17 (27%) had no evidence of vegetations. In two patients, vegetations were noted two and four weeks respectively after an initial echocardiogram had shown no evidence of vegetations. In 27 patients, the echocardiographic diagnosis of vegetations was subsequently confirmed at surgery or necropsy. Two patients had vegetations which were missed by echocardiography, and one patient had thickened aortic valve leaflets incorrectly diagnosed as vegetations. Eight patients were confirmed as having no evidence of vegetations on echocardiography or at surgery (true negative test). In 24 patients there was no confirmation of the presence or absence of vegetations.

Using the standard formulae, the sensitivity of cross sectional echocardiography in diagnosing vegetations was 93% and the specificity 89%. The predictive value of a positive test was 96% and the predictive value of a negative echocardiogram for the absence of vegetations 80%.

The aortic and mitral valves were most commonly affected, with vegetations occurring with similar frequency in either of these positions (Table 1). The underlying pathology predisposing to endocarditis in these patients was similar in patients with vegetations and in those without (Table 2). Three patients had echocardiographic evidence of mitral valve prolapse with redundant leaflet tissue, such that there was difficulty in differentiating coexisting vegetations. In each case, however, there were considered to be vegetations in addition to leaflet tissue, and this was subsequently confirmed at operation in two of the three patients. Other complications were detected by cross

Table 3 *Organisms detected in 62 patients with infective endocarditis. Figures are numbers of patients*

Organism	*With vegetations (n=45)*	*Without vegetations (n=17)*
Streptococcus viridans	8	6
Streptococcus sanguis	3	1
Streptococcus mitis	1	0
α Haemolytic streptococcus	3	0
Streptococcus faecalis	1	1
Streptococcus bovis	1	0
Staphylococcus aureus	13	2
Staphylococcus epidermidis	2	0
Coxiella burnetii (Q fever)	3	0
Haemophilus influenzae	1	2
Corynebacterium diptheriae gravis	1	0
Actinobacillus actinomycetemcomitans	1	0
Paecilomyces varioti (fungal)	1	0
Culture negative	6	5

sectional echocardiography including pericardial effusion in 11 patients, para-annular aortic abscesses in two, and an aortic false aneurysm in one.

Table 3 shows the organisms detected. *Staphylococcus aureus* was more common in the group of patients with vegetations. The other organisms were similar in those with and without vegetations.

Table 4 shows the incidence of clinical complications in these patients. The indications for surgery in all cases were progressive valvar incompetence, severe or refractory heart failure, or uncontrolled infection despite adequate antibiotic treatment. Aortic valve replacement was performed in 25 patients, and mitral valve replacement in nine. Medical treatment alone was successful in eight of the 17 patients (47%) without vegetations but in only 12 of 45 (27%) with vegetations ($p=0{\cdot}09$).

Embolism occurred from the aortic valve in 11 and from the mitral valve in nine. Nine of the 23 patients with embolism had *Staph aureus* infection, including four of those who died. The most common site of embolism was cerebral (12 patients) followed by coronary and renal (five each), and three patients with right heart endocarditis had multiple septic pulmonary emboli. The overall mortality rate was 19%, all deaths occurring in the group with vegetations. Eight of the 12 deaths were directly related to systemic embolism. Four deaths occurred in the group that was treated surgically. Two patients sustained cerebral emboli at the time of operation, and both subsequently died. Two patients died postoperatively with disseminated coagulopathy and renal failure.

Table 4 *Incidence of complications in 62 patients with infective endocarditis. Figures are numbers (%) of patients*

Complication	*With vegetations (n=45)*	*Without vegetations (n=17)*	*p value*
Valvar incompetence	40 (89)	15 (88)	NS
Congestive heart failure	26 (58)	9 (53)	NS
Embolism	21 (47)	2 (12)	<0·01
Death	12 (27)	0	<0·02
Need for surgery	24 (53)	9 (53)	NS

NS, not significant.

Table 5 *Relation of size of vegetation with clinical complications in 45 patients with vegetative endocarditis. Figures are numbers of patients*

Complication	*Size of vegetation (mm)*		
	Small (≤5) (n=4)	*Moderate (6–19) (n=25)*	*Large (≥20) (n=16)*
Valvar incompetence	3	23	14
Congestive cardiac failure	1	15	10
Embolism	0	12	9
Death	0	7	5
Need for surgery	2	12	10

The size of the vegetation on echocardiography was related to the major complications (Table 5). In the group with vegetations, embolism or a fatal outcome in our series occurred only in patients with a vegetation >5 mm in diameter, though two patients without vegetations had systemic emboli. Six patients had sessile vegetations, and embolism occurred in one of these; the remaining 39 patients had mobile pedunculated vegetations. Because of the retrospective nature of this study the size of the vegetations estimated echocardiographically and at surgery or necropsy could not be compared. Nevertheless, in all cases in which there was confirmation of the vegetation available the location and morphology of the vegetation were accurate.

Discussion

The incidence of vegetations in 73% of the patients in our study resembles closely that reported in other studies using cross sectional echocardiography[4 5 11] and is higher than that reported using M mode echocardiography.[1 4 6] The difference in the results of the two methods is most likely to be related to the higher sensitivity of cross sectional echocardiography in detecting smaller and less accessible vegetations, a view shared by others.[4–6] Although somewhat limited by the relatively small number of patients in the present study, the specificity, sensitivity, and diagnostic accuracy support the concept that cross sectional echocardiography is reliable and accurate in detecting vegetations in patients who have active endocarditis. The site and morphology of vegetations seen by echocardiography were related closely to the surgical and necropsy findings. In the two patients who had vegetations missed by echocardiography, one had undergone the investigation six weeks before operation, and thus the vegetations may have developed during this interval; in the other there were abnormal, thickened, fibrotic aortic valve leaflets that made the vegetations difficult to identify. A further patient had thickened calcified aortic valve leaflets that were mistaken for vegetations. Three patients had mitral valve prolapse with redundant leaflet tissue in whom the identification of separate vegetations was difficult, a problem also experienced by others.[12 13]

Cross sectional echocardiography was useful not only in detecting vegetations but also in diagnosing other cardiac complications of infective endocarditis including pericardial effusion and aortic para-annular abscesses. The assessment of left ventricular dimensions and function was also of major benefit in assessing haemodynamic function and frequently averted the need for preoperative cardiac catheterisation in this group of critically ill patients.

Vegetations were found with a similar frequency on the aortic and mitral valves, and complications from either site occurred equally. This contrasts with the findings of Come *et al*, who found a higher incidence of complications from aortic vegetations,[14] though this was not the experience of others.[1 2 7] The organisms detected were similar in patients with and without vegetations, apart from the higher incidence of *Staph aureus* in those with vegetations. Takeda *et al* reported a similar finding.[5]

The incidence of valvar incompetence, congestive heart failure, and the need for surgical intervention was similar in patients with and without vegetations. Lutas *et al* also found a similar incidence of these complications in the two groups in their series of 77 patients.[7] This contrasts with several previous studies that reported a higher prevalence of these complications in patients who had vegetations.[1–3] This difference could be explained by the suggestion that cross sectional echocardiography is more sensitive in detecting smaller and anatomically less accessible vegetations, which are less likely to cause valve destruction and the consequent haemodynamic disturbances. We cannot exclude, however, the possibility that differences in referral patterns or in patient populations may be responsible for the variation in the results of these studies.

The incidence of embolism and the mortality rate were both related to the presence of vegetations on echocardiography, a finding shared with several previous studies.[3 5 14] Almost half the patients with vegetations in our series subsequently had emboli, and the majority of deaths were directly related to systemic embolism (eight of 12). The size of the vegetations was also relevant in that no emboli occurred in patients who had a vegetation that was ≤ 5 mm, though two patients had no vegetations and suffered emboli. The morphology of the vegetations was much less helpful in predicting complications. Medical treatment alone was successful less often in those with vegetations (29%) than in those without (47%), though this difference was not statistically significant. In the group with vegetations, 19 patients who suffered emboli did so during medical treatment, and six of these subsequently underwent valve replacement. Two patients treated surgically had emboli perioperatively that were possibly related to dislodgement of vegetative material during excision of the infected valve. Thus medical treatment was more likely to be complicated by embolism. Four deaths occurred in the surgically treated group of 24 patients compared with eight in the 21 patients treated medically.

These findings considered together suggest that the presence of large vegetations detected by cross sectional echocardiography identifies patients with infective endocarditis who have a high incidence of embolic complications and death. We recommend that early surgery is considered in patients with infective endocarditis and large vegetations in view of this high risk of embolism. The decision regarding surgery, will, however, remain an individual one based on all the clinical aspects of each case.

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Pre-excitation due to accessory sinoventricular connexions associated with coronary sinus aneurysms

A report of two cases

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SUMMARY Ventricular pre-excitation occurred in two cases in which the accessory pathways between the atria and the ventricles were histologically identified as being associated with aneurysmal malformations of the coronary sinus. In one case the connexions were in the posterior wall of the coronary sinus aneurysm and were not related to the atrioventricular annulus; in the other, a connexion was situated in the anterior wall of the aneurysm in close apposition to the annulus and superficially resembled a Kent fibre. These connexions were considered to be of sinus venosus origin and to represent a modification of the muscular sheath that normally surrounds the coronary sinus but does not continue along the coronary veins. One of the posterior wall connecting bundles was composed of abnormally large Purkinje-like fibres; this may have played some role in the manifestation of the pre-excitation by reducing any mismatch impedance.

In normal circumstances the heart beat is initiated in the sinoatrial node and the impulse spreads through the atrial muscle to reach the atrioventricular node where it is delayed before passing on to the ventricular muscle through the atrioventricular bundle of His and the right and left bundle branches. This provides the only functional connexion between the inlet and outlet chambers of the heart. Pre-excitation[1] is said to occur when the ventricular response to the atrial contraction occurs earlier than would be expected if the activation had followed the usual pathway through the specialised conduction system; it is manifested by an unduly shortened PR interval on the electrocardiogram.

Various accessory pathways and connexions have been postulated or described as substrates of the various presentations of this condition (Fig. 1). Accessory atrioventricular muscle fibres bridging the fibrous tissue between atrial and ventricular myocardium may be parietal, as first described by Kent,[2–7] or septal.[8 9]

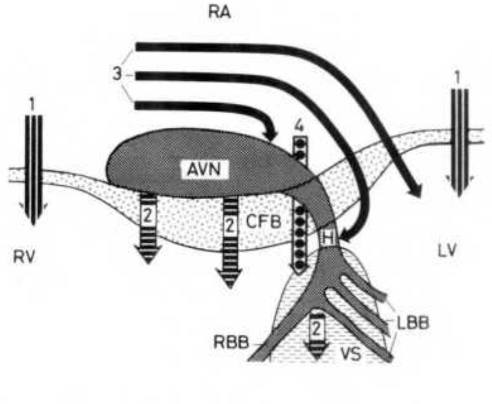

Fig. 1 *Diagram showing normal and abnormal atrioventricular conduction pathways. The normal pathway is from the atrioventricular node (AVN) through the atrioventricular bundle of His (H) which penetrates the central fibrous body (CFB) and divides into the right and left bundle branches (RBB, LBB) in the ventricular septum (VS). Abnormal pathways include 1, Kent fibres; 2, Mahaim fibres; 3, James fibres, and 4, central atrioventricular pathway as described by Krikler et al.*[9] *RA, right atrium; RV, right ventricle; LV, left ventricle.*

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Accessory nodoventricular connexions, between parts of the atrioventricular node and the ventricular myocardium, were first described by Mahaim.[10–12] Bypass tracts or atriofascicular fibres passing from the atrial muscle to the atrioventricular bundle of His have been described by James,[13] and fasciculoventricular connexions between the atrioventricular bundle and the ventricular muscle are included in the connexions described by Mahaim.[10–12] The preferred anatomical terminology is that proposed by the European Study Group on Pre-excitation,[14] as there is considerable confusion and inaccuracy in the use of the various eponymous terms.[15]

When the depolarising impulse reaches the ventricular muscle other than through the atrioventricular bundle and its branches, the spread is abnormal; this is reflected in an abnormal slurring of the first part of the electrocardiographic ventricular complex, the so called delta wave. This, together with the short PR interval, is characteristic of the Wolff-Parkinson-White syndrome.[16] The nature of the polarity of the delta wave in the various electrocardiographic leads enables the site of the epicardial atrioventricular connexion to be determined.[17] When the atrioventricular node is bypassed, but the spread of stimulus within the ventricle is through the atrioventricular bundle and bundle branches, then the short PR interval is followed by normal ventricular electrocardiographic complexes as in the Lown-Ganong-Levine syndrome.[18] Apart from the ventricular pre-excitation these various accessory pathways also provide the substrate for re-entry phenomena; these can lead to arrhythmias, which are the usual mode of clinical presentation of these syndromes. Associated anomalies have been noted, especially Ebstein's malformation of the tricuspid valve[19] and hypertrophic cardiomyopathy.[20]

We studied two cases of clinically documented ventricular pre-excitation syndrome of the Wolff-Parkinson-White type, in which there were unusual aneurysmal malformations of the coronary sinus. In both cases accessory muscular atrioventricular connexions were found within these lesions. As far as we are aware neither the coronary sinus anomaly nor this type of accessory connexion has been described previously.

Case reports

CASE 1

Clinical features

A 16 year old male dyestuffs laboratory technician presented with an eight month history of episodes of palpitation accompanied by retrosternal chest pain. The first episode lasted for about four hours. The duration of the attacks had dimished to about 30 to 45 minutes, but the frequency had increased to every three or four weeks, usually occurring after exercise. There was no relevant medical or family history; he smoked 10–15 cigarettes a day and his consumption of tea, coffee, and alcohol was moderate. Physical examination, chest radiography, and M mode and cross sectional echocardiography were all normal. Standard electrocardiography (Fig. 2) showed the appearances of a Wolff-Parkinson-White pre-excitation syndrome with a short PQ interval, and the polarity of delta waves in the various leads was in accord with anomalous atrioventricular conduction through an accessory pathway in the posterior aspect, according to the table of Gallagher *et al*[17] (Fig. 3).

Treatment was started with disopyramide 100 mg and amiodarone 200 mg twice a day, and he remained well for three months when he had a further spontaneous episode of supraventricular tachycardia that required electrocardioversion. His medication was increased to disopyramide and amiodarone 200 mg each three times a day and he remained symptom free for a further six months, when he experienced another episode of supraventricular tachycardia; this responded to 5 mg verapamil intravenously. The dose of amiodarone was increased to 200 mg four times a day, and he remained well apart from two brief episodes of supraventricular tachycardia which ceased spontaneously. No episodes of atrial fibrillation or atrioventricular dissociation were noted. Graded exercise did not provoke arrhythmia.

In view of the satisfactory response to medical treatment surgery was not contemplated and electrophysiological studies were not performed. In January 1982, three years after the onset of his symptoms, he suddenly collapsed and died while walking in the street. He was 18½ years old.

Necropsy findings

Apart from the presence of a 125 g benign thymoma in the upper part of the anterior mediastinum, abnormal findings were limited to the heart. This was of normal shape, slightly enlarged (130×100×70 mm) and weighed 360 g. The apex was directed normally to the left. The pulmonary and systemic venous connexions appeared to be normal.

The atria were of solitus configuration and of equal size and normal anatomy. A 5 mm diameter 12 mm long tunnel passed upwards from the fossa ovale into the septal wall of the right atrium, but there was no communication with the left atrium. The atrioventricular valves were normal.

The right ventricle wall was slightly thickened to 8 mm and the trabeculations were well marked. The posterior papillary muscle was very small. The left ventricular myocardium and the ventricular septum were uniformly thickened to 20 mm. The free wall

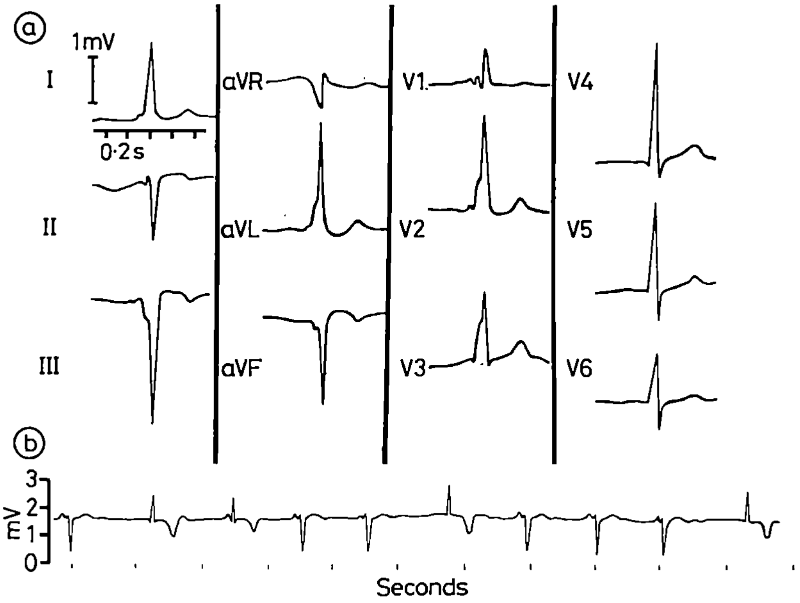

Fig. 2 *Case 1: (a) standard lead of electrocardiogram and (b) rhythm strip.*

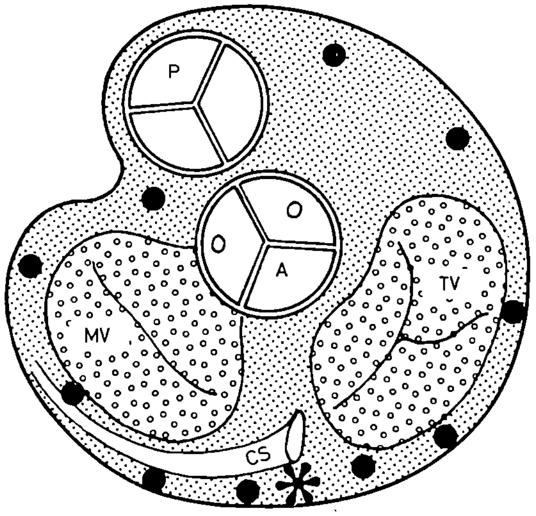

Fig. 3 *Diagram of heart base showing position of various parietal atrioventricular accessory connexions. The asterisk indicates the position of the accessory connexion in cases 1 and 2 according to the electrocardiographic delta wave polarity. A, aorta; P, pulmonary artery; MV, mitral valve; TV, tricuspid valve; CS, coronary sinus.*

was appreciably trabeculated, the papillary muscles ill defined, and many of the mitral valve chordae inserted directly into the ventricular wall.

On the posterior aspect of the heart at the base of the right ventricle immediately below the atrioventricular sulcus, there was an area of cyst-like softening discernible only by palpation and without any visible indication. This occupied an ill defined area approximately 20 mm in diameter and appeared to have no tension within. Incision and subsequent complete opening showed this to be a rather more extensive lesion, extending 50 mm laterally to the right from the midline, 20 mm downwards from the atrioventricular sulcus and up to 10 mm in depth. There was partial division of the cavity by incomplete septa between the anterior and posterior walls, and the cavity was lined by a thin smooth membrane. At the upper left margin, that is approximately in the midline of the heart, this cavity communicated with the lumen of the apparently normal coronary sinus which was 4 mm in diameter and opened into the right atrium through a dilated coronary sinus orifice of 8 mm in diameter. This lesion appeared to be an abnormal (aneurysmal) posterior coronary vein (Fig. 4). The posterior wall was thin and membranous but contained extensive areas of muscle which appeared to continue into the myocardium of the wall of the right ventricle. Dissection and transillumination showed some apparent strands of muscular continuity between the posterior wall of the right atrium, the posterior wall of the coronary sinus, and the posterior wall of this ventricular venous "cyst." Dissection and transillumination of the atrioventricular rings elsewhere showed no evidence of atrioventricular muscle continuity when viewed macroscopically or with a ×5 dissecting lens.

The great arteries arose normally and the pulmonary artery and aorta were each 20 mm in diameter

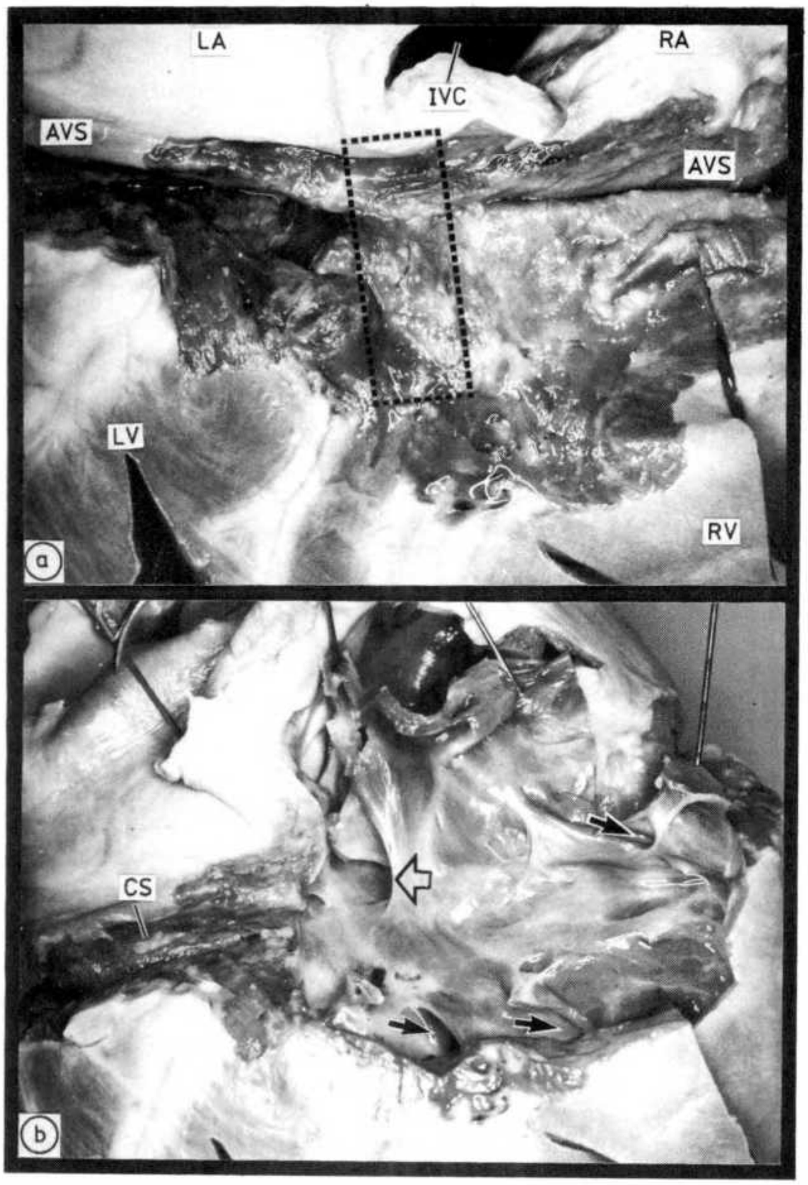

Fig. 4 *Case 1: morphological appearance of the posterior aspect of the heart. (a) The visceral pericardium has been stripped from an area approximately equal to the extent of the coronary sinus aneurysm; the dotted area indicates the block of tissue which was taken for histological sections. (b) The posterior wall of the aneurysm has been incised and reflected upwards showing the smooth partially septated inner aspect. The opening into the right atrium is indicated by the open arrow; openings of the coronary veins are indicated by the small arrows. CS, coronary sinus; RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; IVC, inferior vena cava; AVS, atrioventricular sulcus.*

and had normal valves. The coronary arteries were normal in distribution and structure.

Histology

Serial sections showed the atrioventricular node, the atrioventricular bundle (of His), and the left bundle branch fascicles to be normal. The right bundle branch was slightly abnormal in that its origin and course were situated entirely intramuscularly, and there were early tenuous connexions between it and the working myocardium of the upper part of the atrioventricular septum. A block of tissue was removed from the posterior wall of the coronary sinus aneurysm, as indicated in Fig. 4, extending from the left atrium to the left ventricle. Serial histological sections showed three bands of direct atrioventricular muscular connexion, two of which are illustrated in Figs. 5 and 6. One of these accessory connexions was of special interest as it was composed of very large fibres up to 50 μ in diameter, almost four times the width of the adjacent normal myocardial fibres (10–14 μ). These fibres also showed increased spacing of

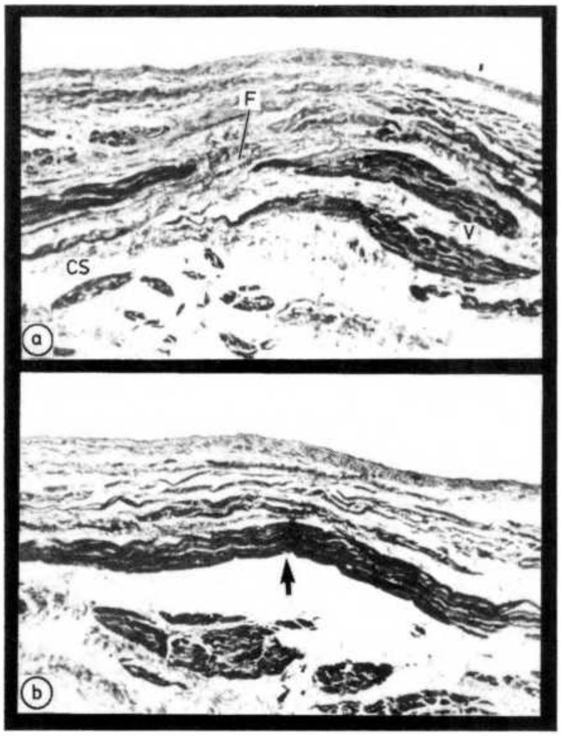

Fig. 5 *Case 1: serial histological sections from the block indicated in Fig. 4a. (a) The muscle fibres of the coronary sinus (CS) and the ventricle (V) are separated by a fibrous zone (F). (b) The same area as (a) at an interval of 40 μ showing the bridging continuity of a muscle strand. (Masson's trichrome stain × 20.)*

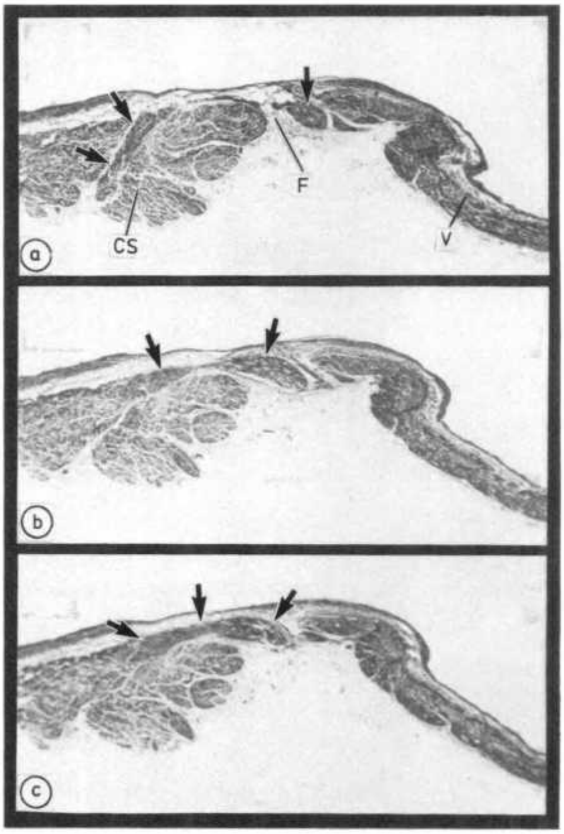

Fig. 6 *Case 1: serial histological sections at 10 μ intervals ((a)–(c)) showing progressive bridging of the fibrous gap by coalescence of two portions of a prominent and discrete muscle band (arrowed). (Masson's trichrome stain × 20.) CS, coronary sinus; F, fibrous zone; V, ventricle.*

the myofibrils and some clear vacuolation, and they were surrounded and separated by conspicuous fibrosis. The appearances were somewhat similar to those of Purkinje fibres (Fig. 7).

CASE 2

A young girl had had a normal history apart from recurrent urinary infections associated with slight ureteric reflux since the age of 7 years. When she was 10 years old she fainted after running uphill but remained well otherwise. Six months later, however, while running at play, she suddenly collapsed, stopped breathing, and went into a tonic convulsion. She was given mouth to mouth artificial respiration during transport to hospital, where on arrival she was pulseless and without an audible apex beat. Respirations were gasping and there had been some inhalation of vomit and she was immediately intubated. An electrocardiogram showed ventricular fibrillation; this reverted to sinus rhythm after electrocardioversion and an initial sinus bradycardia responded to atropine. She remained in sinus rhythm with a good cardiac output and made a full clinical recovery within 24 hours.

Over the next year she experienced several episodes of feeling faint, associated with pallor and palpitation, always after exercise. Several attempts were made to reproduce an attack with exercise in the hospital outpatient clinic but without success. The resting electrocardiogram did, however, show the classical appearances associated with the Wolff-Parkinson-White pre-excitation syndrome with a posterior accessory atrioventricular connexion (Fig. 8).

Almost a year after her initial cardiac arrest she again felt faint while playing in the garden, and this was accompanied by central chest pain. She was

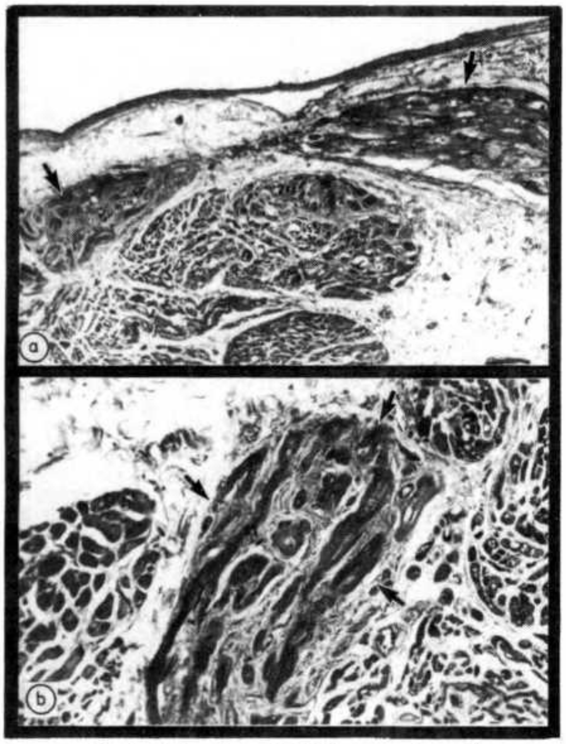

Fig. 7 *Histological sections: (a) high power view of the bridging band (arrows) shown in Fig. 6b showing the contrast between it and the adjacent working muscle. (× 80.) (b) detailed higher power view of part of the anomalous band (arrows) shown in Fig. 6a showing the greatly enlarged muscular elements separated by fibrous stroma. (× 200.)*

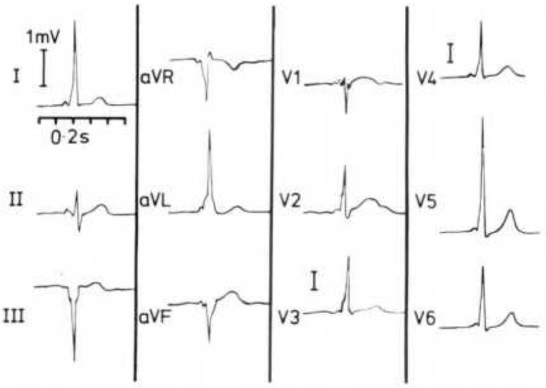

Fig. 8 *Case 2: standard lead electrocardiogram. (Note leads V3 and V4 are recorded at half sensitivity.)*

immediately taken to hospital and on arrival she was pale and restless, and her pulse was noted to be slow and irregular. While being examined she had a cardiac arrest, again associated with a tonic convulsion. The electrocardiogram again showed ventricular fibrillation; this did not respond to electrocardioversion, she proceeded to asystole, and all attempts at resuscitation failed. She was 11 years old when she died.

Necropsy findings

No major abnormalities were noted other than in the heart. The heart was not enlarged, and the cavities, valves, and great vessels were normal. An incision across the posterior wall of the left atrioventricular ring showed a thin walled aneurysmal sac 1 cm across which communicated with the coronary sinus through a narrow slit (Fig. 9). Lateral to this sac the sinus was absent, and the posterior cardiac vein was enlarged and extended towards the apex of the ventricle.

Histological sections traced a very large muscle connexion which slanted diagonally on the posterior wall of the heart, from the posterior wall of the left atrium to the left ventricle across the aneurysmal portion of the coronary sinus (Fig. 10).

Discussion

Accessory atrioventricular connexions and bypass tracts, of the types previously described, are common vestigial remnants of embryonic structures, but only a small proportion of these cause ventricular preexcitation detectable by electrocardiography and very few cause symptomatic disease.[19–21] It is not generally realised that apart from atrioventricular connexions, normal or anomalous, of specialised or nonspecialised myocardium, there is another potential

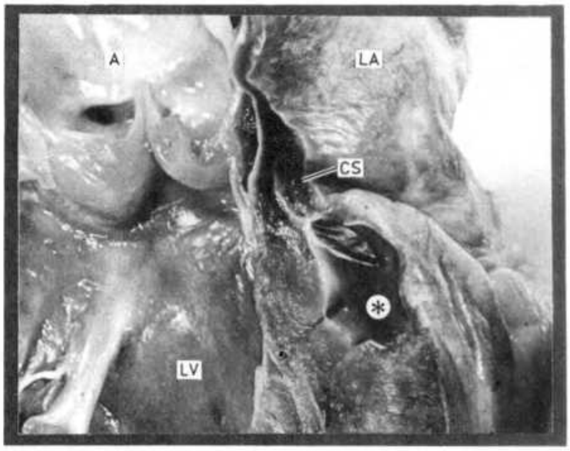

Fig. 9 *Case 2: morphological appearance of the posterior aspect of the atrioventricular junction sectioned in the sagittal plane showing the coronary sinus aneurysm (asterisk) and the slit like orifice into the coronary sinus (CS). LA, left atrium; LV, left ventricle; A, aorta.*

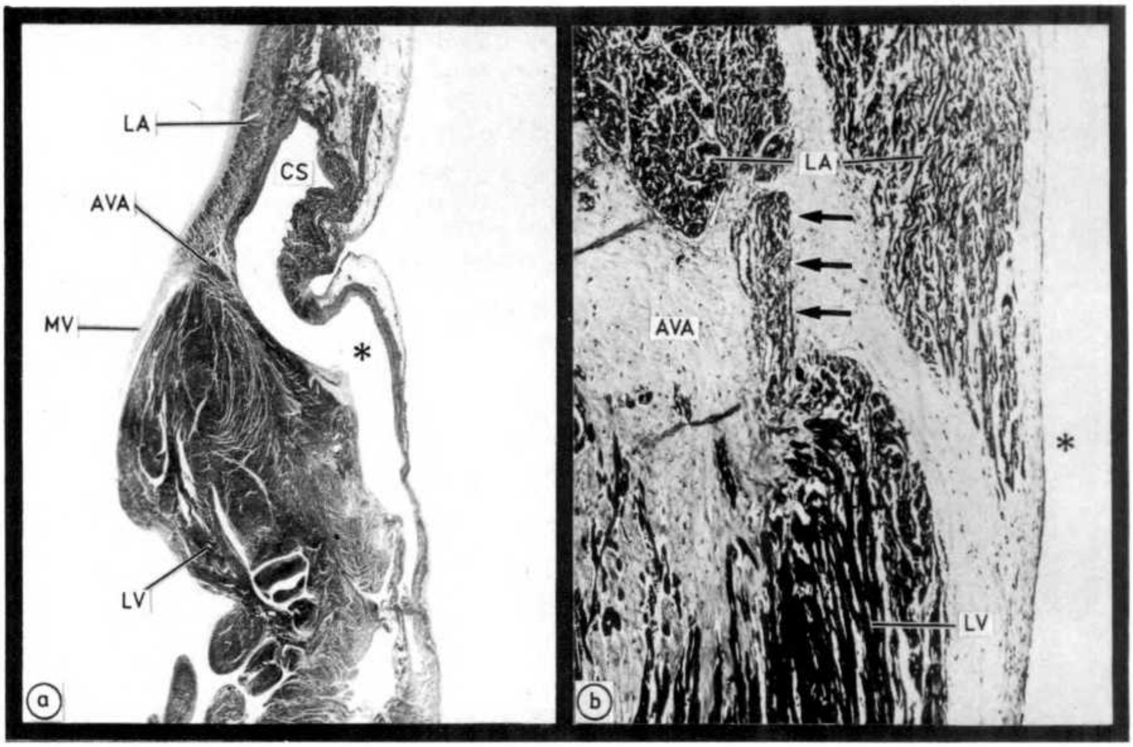

Fig. 10 *Case 2: (a) a longitudinal histological section through the coronary sinus (CS) aneurysm and the adjacent atrioventricular junction. (Masson's trichrome stain × 4.) (b) Microscopical appearance of the atrioventricular junction in an area adjacent to that in (a) showing the accessory connexion (arrows). (Masson's trichrome stain × 20.) AVA, atrioventricular annulus; MV, mitral valve; LA, left atrium; LV, left ventricle. *, aneurysm cavity.*

avenue of communication between the proximal cardiac chamber and the ventricles and that is through the musculature of the sinus venosus. In many vertebrates the sinus venosus is a distinct contractile chamber. In mammals this separate identity is lost during fetal development, and the sinus venosus becomes absorbed into the right atrium and its muscle becomes continuous with that of the atrium. The right extension of the primitive sinus venosus, or cuvierian duct, becomes the cardiac end of the superior vena cava, and the left extension becomes the coronary sinus (Fig. 11). The proximal portion of the coronary sinus is surrounded by a spiral sheath of myocardium which is continuous with that of the morphological right atrium and is clearly a remnant of the sinus venosus musculature (Fig. 12). This muscle sheath normally stops abruptly at or shortly beyond the orifices of the entering coronary veins, but as these veins progress into intimate anatomical relation with the ventricles it remains possible that extensions of this sinus venosus muscle could be responsible for a physiological connexion. Such a circumstance might well be more likely to occur in association with a malformation of the coronary sinus. This appears to have

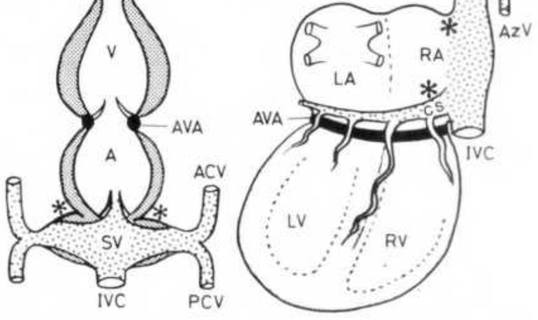

Fig. 11 *Diagrams showing the development of the coronary sinus: (a) schematic early embryonic stage and (b) fully developed condition, as viewed from behind. The sinus venosus component is coarsely stippled. A, atrium; LA, left atrium; RA, right atrium; V, ventricle; LV, left ventricle; RV, right ventricle; SV, sinus venosus; AVA, atrioventricular annulus; SVC, superior vena cava; IVC, inferior vena cava; AzV, azygos vein; CS, coronary sinus; ACV, anterior cardinal vein; PCV, posterior cardinal vein. Asterisks indicate the positions of the sinoatrial and atrioventricular nodes.*

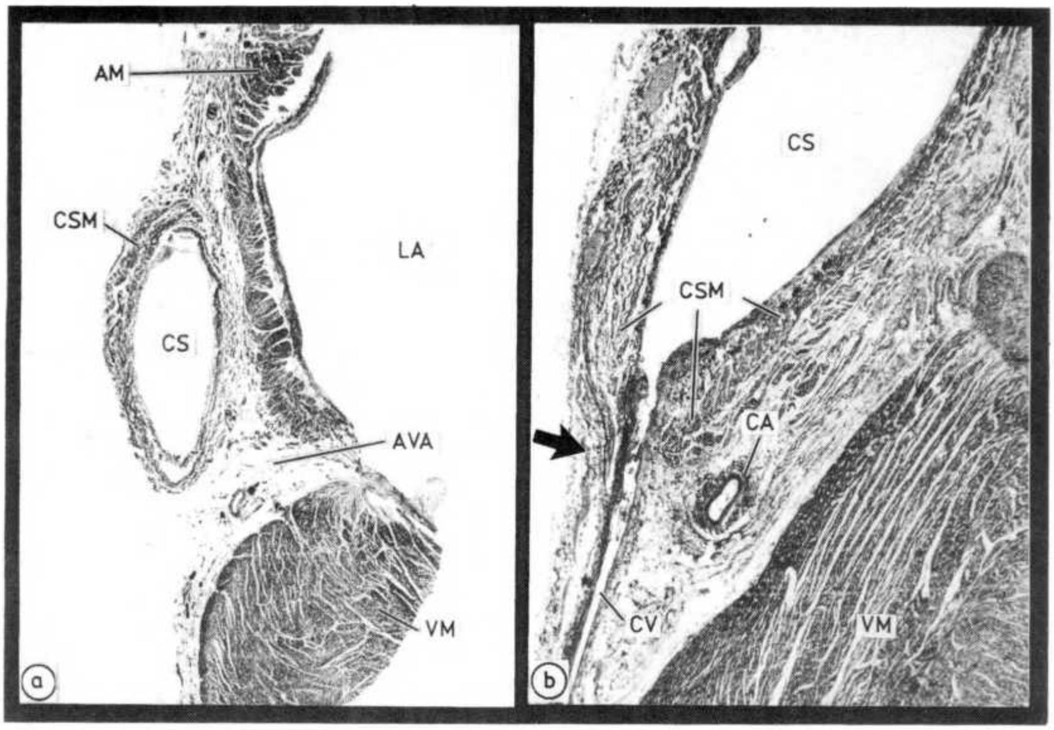

Fig. 12 *Histological sections (a) longitudinally through a normal coronary sinus and adjacent structures and (b) through the origin of a coronary vein from the coronary sinus showing the level of discontinuity of the coronary sinus muscle coat (arrow). (Masson's trichrome stain × 5 (a) and × 20 (b).) CS, coronary sinus; CSM, coronary sinus muscle; AM, atrial muscle; VM, ventricular muscle; AVA, atrioventricular annulus; LA, left atrium; CV, coronary vein; CA, coronary artery.*

been the situation in the two cases which we have studied. In the first case the muscular connexion was located in the posterior aspect of the aneurysm and was not related to the atrioventricular annulus. In the second case the connexion was on the anterior wall of the aneurysm and was in close apposition to the fibrous atrioventricular annulus and presented a histological picture very similar to that of the more usual atrioventricular connexion or bundle of Kent; nevertheless, we consider that the underlying sinoventricular nature was common to both cases (Fig. 13).

The presence of other accessory connexions was not excluded; this would have required serial histological sections throughout the whole of the atrioventricular junction which would have been a formidable task. Dissection with transillumination in the patient in case 1 excluded major connexions, but fibres of microscopic size would not have been identified. Nevertheless, as the electrocardiographic delta wave polarity patterns indicated that the accessory conduction pathways were precisely at the position of the coronary sinus aneurysms, we consider that there is little doubt that the connexions that we identified were responsible for the clinical features in both cases.

The large size of the fibres of one of the accessory connexion bundles in the patient in case 1 is of special interest as a possible contributory factor in the evolution of the clinical abnormality from a pre-existing symptomless anatomical malformation. Accessory tracts are not necessarily used, and Krikler and Rowland have pointed out that narrow pathways may be ineffective in stimulating a ventricular response because of mismatch impedance, in which the "cable capacity" is inadequate to depolarise the large mass of myocardium into which it is inserted.[22] Enlargement of the tracts by muscle disorders such as hypertrophic cardiomyopathy may be a possible cause of activation of such latent pathways by cancelling this mismatch impedance.[23] It is not possible to know whether the Purkinje-type structure of the tract in question had always been so or whether this was an adaptive development in response to the abnormal conduction activity in which it was involved, but in either case such enlargement would be likely to enhance both the conduction rate and the cable capacity. Such changes

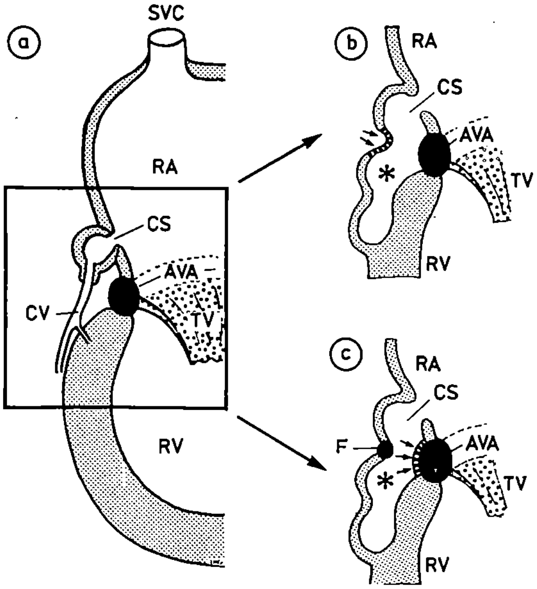

Fig. 13 *Diagrams showing the relation of the coronary sinus muscle to the atrial and ventricular muscle (a) in a normal case, (b) in case 1, and (c) in case 2. The asterisks indicate the coronary sinus aneurysms and the arrows the accessory pathways. AVA, atrioventricular annulus; CS, coronary sinus; CV, coronary vein; F, fibrous discontinuity; RA, right atrium; RV, right ventricle; TV, tricuspid valve.*

have not been described in other accessory pathways, and it is possible that they may be related to the unusual anatomical location.

Although the combination of coronary sinus aneurysm and ventricular pre-excitation is a rare condition, the finding of two almost identical examples within a short period suggests that it is worth bearing in mind especially when cases that are being considered for surgical intervention are investigated, and that during detailed electrophysiological studies placement of the coronary sinus electrode lead could quite conveniently be combined with coronary sinus contrast angiography.

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Tachycardia induced myocardial dysfunction
A reversible phenomenon?

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SUMMARY Four patients with myocardial dysfunction related to tachycardia underwent electrophysiological studies, which showed a re-entrant supraventricular tachycardia using an accessory atrioventricular connexion. Serial assessment of left ventricular function by echocardiography before and after control of the tachycardia indicated a variable degree of reversibility. Endomyocardial biopsy in two patients detected non-specific histological changes. Because of the possible role of ischaemia in this condition effective control of prolonged tachycardia is needed to prevent deterioration of myocardial function.

Paroxysmal supraventricular tachycardia is usually well tolerated in the absence of underlying impairment of cardiac function.[1–3] There are, however, published reports of patients with chronic or frequent episodes of supraventricular tachycardia who present with symptoms and with clinical and radiological signs of congestive cardiac failure.[4–9] The patients in these reported cases were in general young, often in the paediatric age group. Many were without underlying cardiac disease, and with control of the tachyarrhythmia the symptoms and signs of congestive heart failure resolved. Detailed assessment of the mechanism of the arrhythmia and accurate serial determination of left ventricular function before and after the resolution of congestive heart failure, as a result of successful antiarrhythmic treatment, has only recently been reported.[10 11] We report four patients with chronic or frequent episodes of supraventricular tachycardia, resulting in severe impairment of left ventricular function. The mechanism of the arrhythmia was determined in each case by electrophysiological study, and endomyocardial biopsy was performed in two cases. Serial assessments of left ventricular function were made in each case by echocardiography, radionuclide scintigraphy, or both after control of the arrhythmia as well as clinical assessment of symptomatic and functional status.

Patients and methods

CASE 1

A 16 year old girl had an episode of syncope which caused no personal injury. Supraventricular tachycardia (rate 160 beats/minute) was noted at the local hospital, and a chest *x* ray film showed cardiomegaly. She had been asymptomatic up to the time of the accident, and there was no history suggesting a recent viral illness or excessive alcohol consumption. Four weeks later she was referred to the Mayo Clinic with persistent tachycardia. She had remained asymptomatic. Chest *x* ray films showed cardiomegaly without pulmonary congestion, and an electrocardiogram showed a narrow complex supraventricular tachycardia (rate 150 beats/minute) with a long ventriculoatrial interval (Fig. 1). The P waves were negative in leads II, III, and aVF, and the ratio of the interval between the R wave and the retrograde P wave to the cycle length was $>0{\cdot}5$, suggesting the permanent type of reciprocating junctional tachycardia.[12] The left ventricular ejection fraction measured during tachycardia by echocardiography (Fig. 2) and radionclide ventriculography was 29% and 33% respectively The left ventricle was globally hypokinetic, and an echorefractile apical thrombus was noted. There were no other major structural abnormalities of the heart detected by clinical examination or echocardiography. At cardiac catheterisation there were no shunts and the mean pulmonary capillary wedge pressure was 13 mm Hg. A left ventricular biopsy showed mild hyper-

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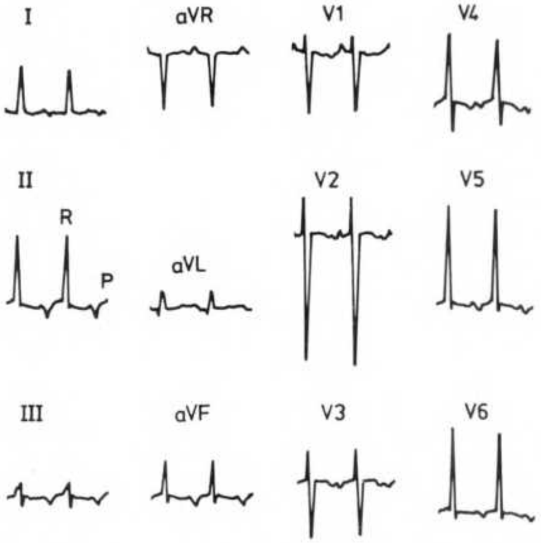

Fig. 1 *Twelve lead electrocardiogram during tachycardia (case 1) showing negative inferior P waves and an RP interval greater than 50% of the RR interval.*

trophy and mild focal interstitial fibrosis.

An electrophysiological study detected a re-entrant supraventricular tachycardia, using a concealed accessory pathway, with earliest atrial activation at the os of the coronary sinus, as has been previously described in this arrhythmia.[12] The supraventricular tachycardia could be easily terminated by ventricular extrasystoles but would spontaneously return after one or two sinus complexes without prolongation of the AH interval. Procainamide terminated the supraventricular tachycardia by abolishing retrograde conduction via the accessory pathway. Subsequent oral treatment with digoxin and quinidine allowed sinus rhythm to return, and a repeat echocardiogram nine days later showed that left ventricular function was unchanged. She was discharged taking digoxin and quinidine and returned for follow up two months later. She had remained in sinus rhythm, and both an echocardiogram (Fig. 3) and radionuclide angiogram showed normal left ventricular function (ejection fraction 60% at rest, 70% at peak exercise). A repeat study one year later in sinus rhythm showed ejection fractions of 53% at rest and of 76% at peak exercise, but the cardiomegaly persisted. The most recent echocardiogram recorded about two and a half years after admission showed normal left ventricular dimensions and function with an ejection fraction of 63%.

CASE 2

A 9 day old boy, born after a normal pregnancy and with a normal delivery, presented with a two day history of poor feeding and irritability. On examination he was in cardiac failure and had a regular narrow complex tachycardia (280 beats/minute). During the following week he had recurrent episodes of supraventricular tachycardia with haemodynamic deterioration. During sinus rhythm, anterograde pre-excitation was noted. An echocardiogram performed in sinus rhythm and with a normal serum bicarbonate concentration showed an ejection fraction of 30%. No other structural cardiac abnormalities were noted clinically or during echocardiography. An electrophysiological study confirmed supraventricular tachycardia using a macrore-entrant circuit with a left lateral accessory pathway as the retrograde limb. The

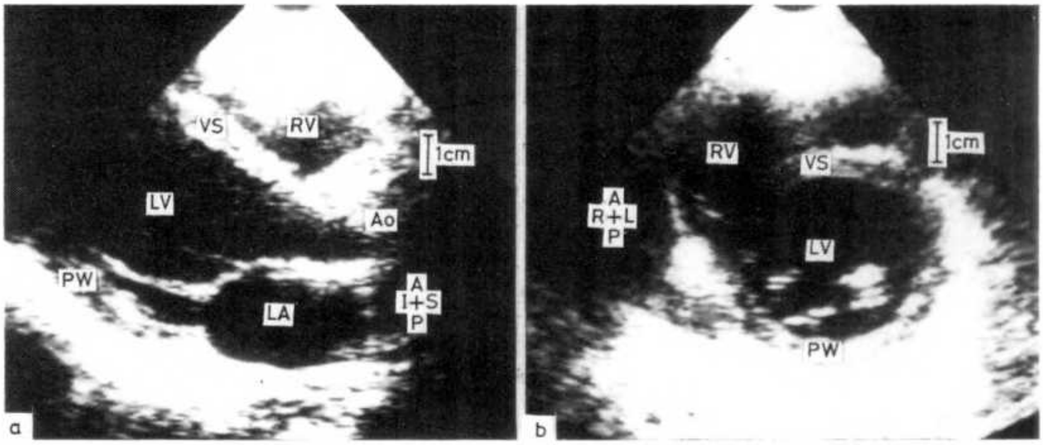

Fig. 2 *Case 1: cross sectional echocardiograms at diastole before tachycardia control in the (a) long and (b) short axis views. End diastolic dimension 60 mm. LV, left ventricle; LA, left atrium; RV, right ventricle; PW, posterior wall; VS, interventricular septum; A, anterior; P, posterior; I, inferior; S, superior; R, right; L, left.*

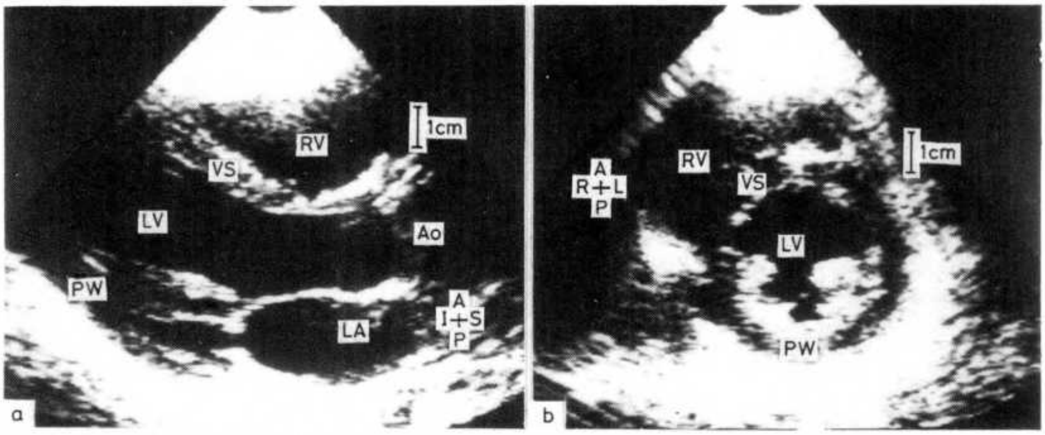

Fig. 3 *Case 1: Cross sectional echocardiograms at diastole three months after tachycardia control in the (a) long axis and (b) short axis views. End diastolic dimension 50 mm. Abbreviations as for Fig. 1.*

arrhythmia was eventually controlled, and six days later a repeat echocardiogram showed a left ventricular ejection fraction of 50%. The child was discharged with treatment and has remained well for four and a half months.

CASE 3

A 3 week old boy, born after a normal pregnancy and with a normal delivery, presented with a two day history of poor feeding. On examination he had a regular tachycardia (280 beats/minute) and was in circulatory shock. He was acidotic, and a chest *x* ray film showed cardiomegaly and alveolar oedema. A narrow complex supraventricular tachycardia was noted on electrocardiography. After cardioversion, sinus rhythm returned (no anterograde pre-excitation) followed by clinical improvement. There was no detectable structural cardiac abnormality on clinical or echocardiographic examination, apart from a global reduction in left ventricular function with an ejection fraction of 10% with a normal arterial pH. During an electrophysiological study a concealed left free wall accessory pathway was shown to participate in the supraventricular tachycardia. Sinus rhythm was maintained with digoxin and quinidine, and a repeat echocardiogram three days later showed normal left ventricular function (ejection fraction 63%). He was well with medication four months after discharge.

CASE 4

A 10 year old boy had had Ebstein's anomaly diagnosed by cardiac catheterisation at the age of 3 years. Since birth he had had infrequent episodes of supraventricular tachycardia, and an electrocardiogram showed anterograde pre-excitation. Evaluation in 1981 by echocardiography and cardiac catheterisation confirmed the diagnosis, and left ventricular function was only mildly abnormal (ejection fraction 48%). He was mildly cyanotic at this time. An electrophysiological study showed two mechanisms for his supraventricular tachycardia: (*a*) macrore-entry using a right free wall accessory pathway retrogradely and (*b*) atrioventricular nodal re-entry using the fast pathway retrogradely. He remained well for two years, being able to play competitive sports. Regular assessments showed good functional status and a normal heart size radiologically. Over a five month period before his most recent admission the episodes of supraventricular tachycardia became more frequent and prolonged, and over the last six weeks his arrhythmia was virtually incessant. Drug treatment (digoxin, propranolol, verapamil, quinidine, encainide) proved ineffective, and he developed worsening cardiac failure and cardiomegaly. Evaluation showed moderate to severe cyanosis and gross cardiac failure. Severe impairment of left ventricular function was noted on echocardiography during sinus rhythm (ejection fraction 20%). Recurrent supraventricular tachycardia (rate 145 beats/minute) with a long VA interval was noted on monitoring. Arterial oxygen saturation was 68%, and left ventricular biopsy showed mild to moderate cellular hypertrophy with focal degenerative changes and mild to moderate interstitial oedema. There was no inflammatory infiltrate. Oral treatment with amiodarone was started, and in four days sinus rhythm was re-established and maintained with pronounced clinical improvement. A repeat echocardiogram three months later showed only a mildly improved ejection fraction of 30% which was unchanged at six months, but at the time of the most recent follow up six months later the ejection fraction had improved further to 40–45%.

Discussion

The effects of chronic or frequent episodes of tachycardia on cardiac function are not well understood. Tachycardia results in an increase in myocardial oxygen demand while causing relative ischaemia due to reduced time spent in diastole. This effect is most prominent in the subendocardium, and, at least in the setting of congestive cardiomyopathy, may possibly result in the observed histological changes of subendocardial fibrosis and cellular vacuolisation as well as depletion of myocardial energy stores.[13] Coleman *et al* induced chronic ventricular tachycardia in dogs with pacing and noted significant reductions in left ventricular function after 2–4 weeks of continuous pacing.[14] This effect persisted after the cessation of pacing. Total myocardial energy stores were also reduced, and this was considered to be related to the impaired myocardial function. Myocardial blood flow was not determined during tachycardia, and the authors remained uncertain as to the cause of the loss of energy stores and impaired myocardial function.

Measurement of coronary blood flow in dogs during atrial tachycardia at rates above 180 beats/minute has shown a 34% reducton in flow.[15] The investigators concluded that this was related to a reduction in aortic pressure and a shortening of diastole. An illustration accompanying the report shows the haemodynamic changes at the onset of tachycardia, accompanied by an electrocardiogram with progressive ST segment depression, suggesting ischaemia.

Direct extrapolation of the data from these animal studies to humans can only be made with caution and reservation. None the less the studies appear to have identified a plausible but unconfirmed explanation for our findings—namely, relative ischaemia despite normal coronary artery anatomy.

If a reduction in coronary blood flow with resultant myocardial ischaemia contributes appreciably to the development of cardiac failure in patients with tachycardia, then such factors as chronicity of tachycardia, rate of tachycardia, anatomical lesions causing reduced myocardial blood flow (for example, coronary artery disease) or increased myocardial oxygen demand (for example, aortic stenosis) and lesions causing arterial desaturation (for example, right to left shunt) might be expected to augment the myocardial depressive effect of tachycardia by accentuating the ischaemic process.

Our first case illustrates the effects of chronic tachycardia. The arrhythmia had been noted for four weeks and, in all likelihood, had been present for longer. Pronounced impairment of left ventricular function both during and soon after resolution of the tachycardia, with subsequent return to normal after two months, suggests a reversible derangement of myocardial cellular function related to the tachycardia. It would seem unlikely that digoxin would account for such a dramatic improvement.[16] Although resting and exercise cardiac function were normal, there was evidence of permanent myocardial functional impairment, with a mild increase in diastolic dimension, and evidence of myocardial fibrosis, without inflammation, on biopsy. None the less at the time of the most recent echocardiogram left ventricular dimensions and overall function had reverted to normal.

In the fourth case frequent prolonged episodes of tachycardia had been occurring for five months, associated with pronounced systemic arterial oxygen desaturation and worsening cardiac failure. Previous evaluations showing near normal left ventricular function and the coincident clinical deterioration imply a detrimental effect of the tachycardia on myocardial function. After resolution of the tachycardia there was only mild improvement in left ventricular function over a nine month period, and an endomyocardial biopsy showed focal severe myocardial damage. Systemic arterial oxygen desaturation in association with tachycardia may have resulted in ischaemia, which led to the observed histological changes, and permanent impairment of myocardial function. Despite the histological appearance there was a further improvement in overall left ventricular function with an increase in ejection fraction to approximately 40–45%, which could reflect a compensatory response from other undamaged areas of the myocardium.

Cases 2 and 3 illustrate the consequences of extremely rapid rates, as are commonly found in infants with tachycardia associated with an accessory atrioventricular connexion. Left ventricular function during sinus rhythm, and in the absence of acidosis, was considerably impaired in both but showed a rapid improvement within one week of controlling the arrhythmia. Whether the immature infant left ventricle is particularly susceptible to the demands of a rapid tachycardia or whether these infants have an underlying left ventricular disorder is speculative, but are intriguing issues which cannot be answered from our observations.

There are several implications of this study. Firstly, chronic or frequent episodes of supraventricular tachycardia can have major deleterious effects on left ventricular function, which may be asymptomatic and transient. Secondly, the effects on left ventricular function are not necessarily completely reversible after control of the arrhythmia and may result in chronic ventricular dysfunction. Thirdly, patients with systemic arterial oxygen desaturation and tachyarrhythmias should be treated promptly to avoid permanent severe myocardial damage. Finally, current knowledge is insufficient to explain the mechanisms of tachycardia induced impairment of left ventricular function and the relation between the biopsy findings and the arrhythmias.

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Disopyramide induced second and third degree atrioventricular block in patients with bifascicular block

An acute stress test to predict atrioventricular block progression

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SUMMARY Syncopal attacks in patients with bifascicular block may be due to both ventricular tachyarrhythmias and intermittent atrioventricular block in addition to non-cardiac causes and lead to antiarrhythmic treatment with drugs or pacemaker or both. The acute electrophysiological effect of intravenous disopyramide 2 mg/kg body weight given over five minutes on the His-Purkinje system was assessed in 27 patients with chronic bifascicular block undergoing evaluation for permanent pacemaker treatment. The predictive value of this pharmacological stress test as regards the development of atrioventricular block during follow up was analysed. The HV interval increased (mean 43%) and the QRS duration was prolonged (mean 24%). Intrahisian or infrahisian second or third degree atrioventricular block occurred in 14 patients after disopyramide administration, requiring temporary pacing in four of them. Before the electrophysiological study 15 of the 27 patients had had at least two syncopal attacks of suspected cardiac origin but no evidence of second or third degree atrioventricular block. Second or third degree atrioventricular block was subsequently recorded in five of these 15 patients during a mean of two years follow up. The sensitivity, specificity, and predictive value of second or third degree atrioventricular block produced by disopyramide administration including subsequent atrial pacing—a positive disopyramide test—as regards later development of atrioventricular block were 80%, 90%, and 80% respectively.

Intravenous administration of disopyramide to patients with bifascicular block and syncopal attacks of suspected cardiac origin may provoke atrioventricular block and asystole requiring immediate temporary pacing. Furthermore, a positive disopyramide test seems to have a significant value in predicting the later development of atrioventricular block.

Bifascicular block (left bundle branch block and right bundle branch block with left anterior or left posterior fascicular block) is associated with an appreciable risk of both ventricular tachyarrhythmias and second and third degree atrioventricular block.[1-3]

Disopyramide is a widely used antiarrhythmic drug with class I and class III properties (Vaughan Williams classification[4]) with a documented effect on ventricular arrhythmias.[5] The safety of intravenous disopyramide infusion in patients with bundle branch block, including those with pronounced infranodal conduction delay, has been claimed.[6] No other similar study has to our knowledge been published. Atrioventricular block progression has on the other hand been reported in one patient with bifascicular block given long term oral treatment with disopyramide.[7]

The purpose of this study was to investigate the short term effect and the potential value in predicting

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Table 1 *Clinical and electrophysiological data on 27 patients with bifascicular block receiving intravenous disopyramide as an acute stress test*

Case No	*Age/sex*	*Cardio-vascular disease*	*Cardio-megaly*	*BFB*	*Electrophysiological study*							*Follow up*				
					Basal state		*Disopyramide*									
					HV (ms)	*Split H wave*	*HV (ms)*	*PPP*	*AP*	*VP*	*DT*	*Duration (mnth)*	*AVB*	*PM*	*Syncope*	*Outcome*
							Group 1									
1	74M	HT	−	RBBB+LAFB	100	−	125	−	−	+	+	21	+	+	−	
2	55M	AMI (1 mnth)	+	RBBB+LAFB	60	+	75	−	+	−	+	23	−	+	−	Died
3	72F	−	−	RBBB+LAFB	80	+	80	+	0	0	+	21	−	+	+	Died
4	74M	−	+	LBBB	30	−	45	−	−	−	+	36	−	+	−	
5	77M	CHF, HT	+	LBBB	65	−	0	+	0	0	+	42	+	+	−	
6	77M	AMI (2 wk)	−	RBBB+LAFB	50	+	65	−	−	−	−	1	−	+	+	Died
7	60M	AMI (3 wk)	+	RBBB+LAFB	50	−	125	+	−	−	+	22	−	+	−	
8	73F	AMI(1mnth)	+	RBBB+LPFB	25	−	35	−	−	−	−	5	−	+	−	Died
9	81M	−	−	RBBB+LAFB	45	−	60	−	+	−	+	1	−	+	−	
							Group 2									
10	71M	−	+	RBBB+LAFB	50	−	100	−	−	−	+	26	−	−	+	Died
11	68M	−	−	RBBB+LAFB	70	−	95	−	−	−	−	31	+	+	−	
12	83M	−	0	RBBB+LAFB	45	−	75	−	−	−	+	26	−	+	−	
13	53M	−	−	RBBB+LAFB	45	−	50	−	+	+	+	44	+	+	−	
14	53M	HT	−	LBBB	95	−	160	+	+	0	+	52	+	+	−	
15	77M	DM	−	RBBB+LAFB	45	+	90	−	−	+	+	7	−	+	−	
16	59M	HT	−	RBBB+LAFB	55	−	70	−	+	−	+	41	+	+	−	
17	70M	−	−	RBBB+LAFB	30	−	55	−	−	+	+	24	−	+	−	
18	62M	−	−	RBBB+LAFB	45	−	60	−	−	+	+	7	−	+	−	
19	62M	−	−	RBBB+LAFB	55	−	75	−	−	−	−	9	−	−	−	
20	74F	−	−	RBBB+LAFB	45	−	75	+	−	−	+	64	+	+	−	
21	70M	CHF	−	LBBB	95	−	105	+	−	−	+	12	−	+	−	Died
22	79M	−	+	RBBB+LAFB	50	−	80	−	−	−	+	20	−	+	−	Died
23	70M	AMI (5 yr)	−	RBBB+LAFB	45	−	65	−	−	−	−	12	−	−	−	Died
24	71M	HT	−	RBBB+LAFB	50	+	55	−	−	−	−	3	−	−	−	
							Group 3									
25	70M	AMI(1mnth)	−	RBBB+LAFB	30	−	50	−	−	−	+	50	−	−	−	
26	52M	AMI(5mnth)	−	RBBB+LAFB	50	−	60	−	−	−	−	53	−	−	−	
27	40M	AMI(1mnth)	+	RBBB+LAFB	30	−	40	−	−	−	−	12	−	−	−	
Mean					53		76					24·6				
Range					30–100		35–160									

Group 1, previously documented second/third degree AV block; group 2, syncopal attacks; group 3, neither syncopal attacks nor previously documented AV block; +, present; −, absent; 0, information not obtained.

BFB, bifascicular block; RBBB, right bundle branch block; LBBB, left bundle branch block; LAFB, left anterior fascicular block; HV, HV interval; PPP, pure pharmacological provocation; AP, atrial pacing; VP, ventricular pacing; DT, disopyramide test; AVB, atrioventricular block; AMI, acute myocardial infarction; HT, hypertension; PM, permanent pacemaker treatment; DM, diabetes mellitus; CHF, congestive heart failure.

the development of atrioventricular block of disopyramide given during an invasive electrophysiological study of patients with permanent bifascicular block undergoing evaluation for implantation of a permanent pacemaker.

Patients and methods

STUDY GROUP (TABLE 1)

The study population consisted of 27 patients (24 men and three women; mean age of 68 (range 40–83; median 70) years) referred to our department for evaluation of the indications for permanent pacemaker treatment or admitted to our coronary care unit with a suspected acute myocardial infarction.

Group 1—Nine patients had documented second or third degree atrioventricular block, either during the acute phase of a myocardial infarction (four patients, cases 2, 6, 7, and 8), or during treatment with digitalis or a beta blocking drug (cases 1 and 9), or occurring spontaneously (cases 3, 4, and 5).

Group 2—Fifteen patients had chronic bifascicular block and at least two episodes of syncope of suspected cardiac origin. A complete history and physical examination supplemented by an electroencephalogram, orthostatic test, and other investigative procedures failed to explain the syncopal attack. Furthermore, at least 24 hours of electrocardiographic recording and exercise tests had not provided evidence of arrhythmias sufficient to explain the syncopal attacks—that is, no second or third degree atrioventricular block or advanced ventricular arrhythmias.

Group 3—Bifascicular block developed in three patients with an acute myocardial infarction. None of them had a history of syncope or previously documented second or third degree atrioventricular block.

The investigation protocol was approved by the medical ethics committee of the hospital and the patients gave their informed consent.

DEFINITIONS

Bifascicular block is defined here as left bundle branch block[8] or right bundle branch block[8] with left axis deviation (−30° to −90°) indicating the presence of left anterior fascicular block, or right axis deviation (+110° to +180° degrees) indicating the presence of left posterior fascicular block. Terms and definitions relating to cardiac rhythm follow the recommendations by Hecht *et al*[9] and Robles de Medina *et al.*[10]

The electrophysiological study was performed with the patient fasting and unsedated, and treatment with cardioactive drugs was withheld for more than five half lives before the investigation. Three pacing leads with a distance of 1 cm between the electrodes were introduced percutaneously under local anaesthesia via a femoral vein. One quadripolar lead was positioned against the lateral wall, high in the right atrium for stimulation and recording. A tripolar lead was placed across the tricuspid valve for registration of the His bundle potential, and a bipolar lead was placed in the right ventricular apex for safety reasons. The intracardiac electrogram and at least surface leads I, II, and V1 were recorded on a Mingograph (Siemens-Elema, Sweden) with frequency limits of 50 and 700 Hz at a paper speed of 100 mm/s. Pacing was performed with a stimulus duration of 2 ms and a voltage of about three times the stimulation threshold using a stimulator for programmed pacing (Devices Ltd, England).

The HV interval was measured from the first rapid phase of the H wave to the earliest ventricular activity in any lead. The QRS duration was measured in lead II. The HV interval and QRS duration were given as the mean of at least three complexes rounded off to the nearest 5 ms. Atrial pacing was performed to determine sinus node recovery times, the atrial rate inducing Wenckebach block, and the atrioventricular nodal refractory period as previously described.[11] Right ventricular pacing (see below) was performed at rates of 100 and 130 impulses per minute for periods of 10 and 30 seconds.

DISOPYRAMIDE TEST

Disopyramide (Roussel Laboratories Ltd, England) 2 mg per kg body weight (without upper dose limit) was given intravenously over five minutes. The duration of the HV and QRS intervals was measured within five minutes of the end of the infusion.

In this study a disopyramide test was considered to be positive in four circumstances. Firstly, the test was positive if second or third degree atrioventricular block appeared after disopyramide administration without any other interference of the spontaneous heart rate (pure pharmacological provocation). Secondly, the test was positive if second or third degree atrioventricular block, intraHis or infraHis, appeared during atrial pacing subsequent to the disopyramide administration.[12] Thirdly, the test was positive if second or third degree atrioventricular block, intraHis or infraHis, appeared after abruptly terminated ventricular pacing subsequent to disopyramide administration. The reason for using right ventricular pacing as a stress test was the observation during the electrophysiological study of one of the first investigated patients (case 13). After disopyramide injection he developed complete infraHis heart block immediately after a spontaneous ventricular extrasystole and subsequently, and in a reproducible manner, after short periods of ventricular pacing. Finally, we also analysed the value of the HV prolongation induced by disopyramide administration. According to previous results the expected prolongation would be on average 20% after the same dosage.[6] We arbitrarily chose a 50% prolongation as the lower limit for a potential predictor.

FOLLOW UP

During follow up the patients were seen three to four times a year, their history assessed, and a standard electrocardiogram recorded. When necessary the pulse generator was set low to elucidate the underlying spontaneous heart rhythm.

STATISTICAL METHODS

Mean values of electrophysiological variables, follow up duration, and number of available electrocardiographic recordings were given as arithmetic means or medians or both as indicated. Student's t test for paired observations was used for comparison of HV and QRS intervals before and after disopyramide administration. The predictive values of the different test variables in relation to the occurrence of second or third degree atrioventricular block were expressed as sensitivity, specificity, and predictive value of a positive test according to Galen and Gambino.[13] Fisher's exact test was used to test the result of the disopyramide test and the disopyramide test combined with an HV interval of ≥70 ms in the basal state in relation to the later development of second and third degree atrioventricular block.

Results

At the beginning of the electrophysiological study all patients had 1:1 conducted sinus rhythm except one (case 5), who had second degree atrioventricular block.

The His-Purkinje conduction time was significantly prolonged, with a mean increase of the HV interval of

43% ($p < 0{\cdot}001$). Two distinct His potentials were recorded in five patients: the H_1H_2 interval increased in three (case 2: 90 ms, case 15: 35 ms, case 24: 10 ms), did not change in one (case 6), and could not be measured in one (case 3) because of complete heart block. In 10 patients the HV prolongation produced by disopyramide was 50% or more (Table 1). The QRS duration was prolonged by a mean of 24% ($p < 0{\cdot}001$).

SECOND AND THIRD DEGREE ATRIOVENTRICULAR BLOCK AFTER DISOPYRAMIDE (TABLE 1)

The disopyramide administration induced intrahisian or infrahisian second (cases 1, 2, 7, 9, 14, 15, 16, 17, 18, and 21) or third (cases 3, 5, 13, and 20) degree atrioventricular block in a total of 14 patients. There was no significant difference in types of bifascicular block.

Group 1—Of the nine patients, six (67%) developed atrioventricular block after disopyramide injection, three from pure pharmacological provocation, two from subsequent atrial pacing, and one after ventricular pacing. Of the other three patients, two had had a myocardial infarction. One patient (case 6) had an anterolateral wall infarction two weeks before the investigation and complete heart block after verapamil treatment for rapid atrial fibrillation. The other patient (case 8) had an infarction of the inferior wall, with involvement of the anterior and lateral parts of the left ventricular wall one month before the study.

Group 2—Disopyramide induced atrioventricular block by pure pharmacological provocation in three patients, by atrial pacing in two (plus one of the previous three), and after ventricular pacing in three (plus one of the two resulting only after atrial pacing).

Group 3—Disopyramide did not induce any atrioventricular block.

In four (cases 5, 7, 13, and 20) of the 14 patients with disopyramide induced second and third degree atrioventricular block, prolonged asystole or haemodynamically inadequate heart rate required temporary ventricular pacing. Adequate spontaneous heart rate resumed within less than one hour. Two of these four patients had no evidence of myocardial or valvar disease. A transient episode of hypotension occurred in one patient (case 7). No other adverse effects were observed.

FOLLOW UP

The patients were followed for a mean of 24 months, during which time eight died, all but one from cardiovascular causes. Ventricular fibrillation occurred in one case of hospital death (case 6). Syncopal attacks during follow up occurred in three patients, one of whom died of an acute myocardial infarction and the others of a stroke.

The patients were seen a mean of 11 times and an electrocardiogram recorded 2–25 times (median 12 available recordings).

Second or third degree atrioventricular block was recorded in two of the nine patients in group 1 during follow up. In five (four of 11 with right bundle branch block with left anterior fascicular block and one of two with left bundle branch block) of the 15 patients in group 2 second or third degree atrioventricular block occurred 3–38 months after the electrophysiological study. In none of the three patients in group 3 was second or third degree atrioventricular block recorded during follow up.

PREDICTION OF ATRIOVENTRICULAR BLOCK PROGRESSION (TABLE 2)

The results of possible prognostic variables and tests—that is, the presence of an HV prolongation to ≥70 ms in the basal state and a positive disopyramide test—were related to the occurrence of second or third degree atrioventricular block.

An HV interval of ≥70 ms in the basal state was seen in five patients, two in group 1 and three in group 2. This finding was a specific (90–92%) but insensitive (29–40%) indicator of previous or subsequent occurrence of atrioventricular block.

The results of the disopyramide test are given separately for the three groups. In this analysis the three different groups served different purposes. Group 1 gave an indication of the sensitivity and group 3 of the specificity of the disopyramide test. Group 2 was then used to define the prognostic or predictive values.

In group 1 a comparison was made with the episodes of atrioventricular block that were recorded before the electrophysiological study. As by definition all these patients had had transient second or third degree atrioventricular block this comparison gave an indication of the sensitivity of the disopyramide provocation. Seven out of nine patients had a positive test, which gave a sensitivity of 78%.

Group 3 on the other hand indicated the specificity of the disopyramide provocation as the patients had neither a history nor symptoms of second or third degree atrioventricular block. One of these three patients had an HV prolongation of more than 50% after disopyramide; otherwise the disopyramide test was negative. Atrioventricular block was not recorded in these patients during 12, 50, and 53 months of follow up.

Group 2 comprised patients in whom a test like the disopyramide provocation would probably have its clinical applicability in the future—that is, as a prognostic test. Initially, the disopyramide test was tentatively considered to be positive in four circumstances.

Table 2 *Prognostic value of different physiological variables and tests in determining previous (group 1) and subsequent (group 2) evidence of second/third degree atrioventricular block*

	Sensitivity (%)		*Specificity (%)*		*Predictive value (%) of positive test*	
	Groups 1, 2, and 3	*Group 2*	*Groups 1, 2, and 3*	*Group 2*	*Groups 1, 2, and 3*	*Group 2*
HV interval ≥70 ms (basal state)	29	40	92	90	80	67
Disopyramide test (DT) and:						
Pure pharmacological provocation (PPP)	43	40	85	90	50	67
PPP and atrial pacing (AP)	64	80*	92	90*	90	80*
PPP, AP, and ventricular pacing	71	80	69	60	71	50
Change in HV interval ≥50%	29	40	54	50	40	29
DT, PPP/AP, or HV ≥70 ms (basal state) or all	—	100**	—	90**	—	83**

*p = 0·017; **p = 0·002 (Fisher's exact one tailed test).

Table 2 shows that the result of ventricular pacing and an HV prolongation of ≥50% after disopyramide injection both had poor sensitivity and specificity for the occurrence of second or third degree atrioventricular block. If, however, a positive disopyramide test was defined as second or third degree atrioventricular block occurring with pure pharmacological provocation and after subsequent atrial pacing the prognostic value of the test is greatly improved—namely sensitivity 80%, specificity 90%, and predictive value of a positive test 80%.

The best predictive value was, however, obtained if an HV prolongation to ≥70 ms in the basal state and a positive disopyramide test were combined. In our group of patients this latter combination gave a sensitivity of 100%, a specificity of 90%, and a predictive value of a positive test of 83%.

Discussion

SHORT TERM EFFECT OF DISOPYRAMIDE

Contrary to previous experience[6] we thus found that the intravenous administration of disopyramide 2 mg/kg body weight can induce second and third degree atrioventricular block in patients with bifascicular block. In the study by Desai *et al* patients with a recent acute myocardial infarction and patients with evidence of second or third degree atrioventricular block were excluded.[6] Sixteen of their 22 patients had bifascicular block and six right bundle branch block. The disopyramide dose was the same, but the infusion rate was seven minutes in their study and five minutes in ours, the difference probably being of little importance. A point of utmost importance is the presence of cardiogenic syncopal attacks, which could either be attributed to ventricular tachyarrhythmias or intermittent second or third degree atrioventricular block. In the report by Desai *et al* the presence or absence of syncopal attacks was not stated.[6] Assuming that none of their patients had had syncopal attacks, their group of patients would be comparable to our group 3, and then no discrepancy in results would exist. It is, however, the patients with syncopal attacks who require most diagnostic and therapeutic consideration.

In two recent reports of patients with bifascicular block and syncope of uncertain origin the ability of subsequently performed programmed stimulation to induce ventricular tachycardias has been taken as evidence for their causative role.[14 15] Our study protocol did not include programmed stimulation for the routine provocation of ventricular tachyarrhythmias, but it was performed in one patient (case 19). In this patient, non-sustained ventricular tachycardias could be induced in the right ventricular outflow tract before, but not after, disopyramide administration. As the disopyramide was well tolerated and the electrophysiological study was otherwise normal, this patient was subsequently prescribed oral disopyramide. He has been free of symptoms during follow up. As regards the other patients, the absence of recurrent syncopal attacks in most cases indicated the absence also of ventricular tachycardias, although it cannot be excluded that this arrhythmia was the cause of the previous syncopal attacks and that spontaneous remission had occurred.

ATRIOVENTRICULAR BLOCK PROGRESSION IN PATIENTS WITH BIFASCICULAR BLOCK

The prevalence of bifascicular block is 1–1·5% in the adult population,[2 16–18] but the yearly incidence of atrioventricular block progression is only 1–4%.[1–3] No clinical or standard electrocardiographic features have been found to predict progress to second or third degree atrioventricular block.[19]

Three principally different electrophysiological factors of prognostic value have previously been identified: *(a)* an HV prolongation in the basal state,[1–3] *(b)* second or third degree atrioventricular block in the His-Purkinje system during atrial pacing,[12] and *(c)* pharmacological provocation of atrioventricular block with procainamide[20] and ajmaline.[21]

The reason for choosing disopyramide in this study was that it has both class I antiarrhythmic properties, like procainamide and ajmaline, and also class III properties and anticholinergic effects.[4] Our hypothesis was that latent His-Purkinje disturbances could be provoked *(a)* by the class I and III antiarrhythmic effects and *(b)* by atrially paced impulses reaching the distal conduction system at higher rates as vagally depressed atrioventricular nodal conduction would be counteracted by the anticholinergic effect. Disopyramide would thus provide an opportunity to combine the principles *(b)* and *(c)* in the previous paragraph.

The occurrence of second and third degree intrahisian or infrahisian atrioventricular block during disopyramide administration may be a provocation of intermittent atrioventricular block, an unmasking of a latent predisposition for atrioventricular block, or an adverse reaction to the drug that is unrelated to prognosis. The critical factor for evaluating the prognostic importance of such a reaction is of course the outcome during follow up. The patients were followed with repeated standard electrocardiographic recordings. This method has, however, obvious limitations in evaluating prognostic tests for the development of atrioventricular block. Jensen *et al* found that more than 50% of patients with third degree atrioventricular block and syncopal attacks had intermittent atrioventricular block and about 75% of the patients in the group with intermittent atrioventricular block had bifascicular block during sinus rhythm.[22] It is therefore possible that we were not able to detect intermittent atrioventricular block in some patients. But even with this reservation, we found the disopyramide test to be of potential value in predicting atrioventricular block progression (Table 2). In our limited group of patients the predictive value of the disopyramide test clearly exceeded the values reported concerning other predictors such as HV prolongation in the basal state,[1-3] intrahisian or infrahisian atrioventricular block during atrial pacing,[12] which did not occur in any of our patients, and the value of the ajmaline test.[21] The validity of the results of the disopyramide test must, however be evaluated in a prospective study of a larger group of patients. The use of a bradycardia indicating pacemaker[23 24] would then offer a safe and sensitive method for detecting clinically significant permanent or intermittent bradycardias due to atrioventricular block.

If we analyse the results in the group of patients with a previous acute myocardial infarction the disopyramide test seems to have a limited value. The number of patients is, however, small, and the interval between the infarction and the electrophysiological study differs. Two patients (cases 2 and 7) with a false positive disopyramide test as regards later atrioventricular block development were studied three weeks and one month after the infarction, which may be too early.

ADVERSE EFFECTS

An adverse effect of disopyramide administration was seen in one patient. He had before the study had a massive anterior myocardial infarction and was mobilised but not haemodynamically entirely stabilised. This patient was one of the four who required temporary pacing. The pronounced but transient fall in blood pressure was probably due to a combination of inadequate heart rate and impaired ventricular performance which was further depressed by the negative inotropic effect of disopyramide.[25]

CONCLUSION

The acute intravenous administration of disopyramide to patients with bifascicular block may induce second and third degree atrioventricular block both in patients with previously documented transient second or third degree atrioventricular block and in patients with a history of syncope of suspected cardiac origin. Furthermore, this procedure can be used as a stress test of the His-Purkinje conduction system in the latter group of patients and seems to have a potential value in predicting subsequent development of second or third degree AV block.

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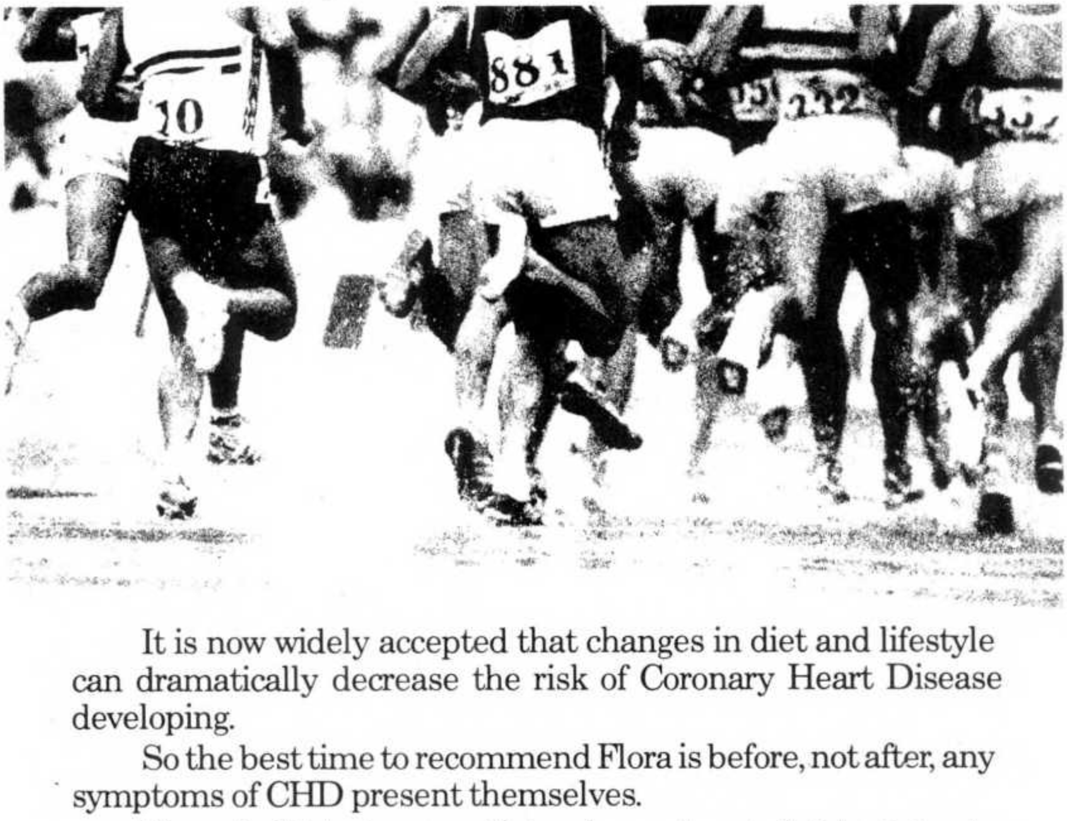

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Tillotts

Br Heart J 1985; 53: 335–6

New guidelines for training in adult cardiovascular disease

Guidelines

Adult cardiology

GENERAL PROFESSIONAL TRAINING

Three years general medical training. Specialisation in cardiovascular medicine without an adequate period of general medical training is discouraged. Research experience may be appropriate before beginning higher specialist training.

HIGHER SPECIALIST TRAINING

The increasing need for cardiological expertise in the district general hospital (DGH) coupled with other factors such as the decreasing reliance on cardiac catheterisation have rendered the separate senior registrar training programmes for physician-cardiologists in the DGH and for cardiologists in the specialist centre inappropriate. They are now replaced by a single training programme for the spectrum of existing consultant posts in cardiovascular medicine and cardiology.

Overlap of and variation in the components of the training programme must be allowed in the interests of flexibility and in order to cater for the talented individual with unorthodox experience and approaches. For example, obligatory cardiology and general (internal) medicine (G(I)M) training may be undertaken simultaneously provided that the overall amount of training is as specified below. The circumstances and requirements of individual departments and hospitals will be taken into account and, as usual, ad personam approval will be considered for special cases.

(i) Obligatory cardiology training—Of the four years required for specialist training, at least two years should be spent in active clinical participation as senior registrar in a specialist cardiac centre, including at least one year in a centre with cardiac surgery. During this time the specialist training should be based on clinical experience in general cardiology (inpatient and outpatient care), and should include training in cardiac catheterisation and angiography, echocardiography, ambulatory monitoring, cardiac pacemaking, exercise stress testing, nuclear cardiology, acute coronary care, and the care of patients before and after cardiac surgery.

(ii) Obligatory G(I)M training—One year or its equivalent should be spent in a post approved for higher medical training in general medicine.

(iii) Fourth year—A further year of this higher medical training programme should not be spent undertaking service cardiology but should offer the opportunity for experience in one or more related fields which is of benefit to the trainee wishing to practise general and cardiovascular medicine, eg general medicine, hypertension, pharmacology, epidemiology, cardiac rehabilitation, cardiovascular research. Up to one year of this experience would be eligible for retrospective accreditation, whereas the obligatory training requirements listed in (*i*) and (*ii*) above would normally be after appointment as senior registrar.

(iv) The senior registrar training programme must include adequate opportunity for research.

(v) The senior registrar training must include a regular teaching commitment.

Paediatric cardiology

GENERAL PROFESSIONAL TRAINING

Should include six months neonatal paediatrics, six months in general paediatrics, and one year in adult or paediatric cardiology.

HIGHER PROFESSIONAL TRAINING

Obligatory experience: four years in approved training in paediatric and adult cardiology progressing towards full specialisation in paediatric cardiology.

Document JCHMT 5/84 (July 1984)

Comments

The specialist advisory committee in cardiovascular disease has recently reviewed the guidelines for specialist training in cardiology. New guidelines have been drawn up over the last two years with the agreement of the British Cardiac Society and its council, the cardiology committee of the Royal College of Physicians, and the specialist advisory committee in general internal medicine. We here briefly outline the functions of the specialist advisory committee and summarise the reasons for the change.

The JCHMT and the SAC

The Joint Committee on Higher Medical Training (JCHMT) is responsible for formulating guidelines for training in the medical specialties, approving posts and training programmes, and granting accreditation. Posts are approved as suitable for specialist higher medical training by the Specialist Advisory Committee (SAC) after considering the reports of visitors and are periodically reviewed. On appointment to an approved senior registrar post an incumbent should apply to the Joint Committee, c/o The Royal College of Physicians, London, for enrolment in the relevant specialties, using forms available from postgraduate deans. Adequacy of general professional training and the possibility of retrospective recognition of accreditable specialist experience will then be assessed. After completion of the training programme of higher medical training, the senior registrar should apply to the Joint Committee for accreditation, using forms likewise available from postgraduate deans.

Reasons for change

The old guidelines recognised two different types of cardiologist—neatly, if invidiously, labelled as types A and B—the former in a specialist centre with cardiac catheter facilities and cardiac surgery, the latter in the district general hospital.

The practice of the specialty has changed considerably. Technological developments have brought much of modern diagnostic cardiology within the capabilities of the district general hospital, where the prevalence and nature of cardiac problems and the extent to which they have become amenable to treatment have brought a need for cardiological expertise. These same developments have generated a workload and subspecialisation in cardiology at regional centres which have tended to separate the specialty from general medicine. A byproduct has been loss of flexibility, with a mismatch between trained senior registrars and available consultant posts.

Present patterns of practice require the appointment of consultants with cardiological expertise to district general hospitals, where they must usually also act as general physicians. Cardiologists in regional centres must likewise be well versed in general medicine. Many cardiologist/physicians at district general hospitals now in fact retain cardiology sessions at their regional centre, while the extent to which the cardiologists at the regional centre practise general medicine and participate actively in cardiac investigation varies with local practice, preference, and seniority. The senior registrar should accordingly be trained for a spectrum of cardiological posts in which to develop his/her special interest as appropriate.

A H Henderson, Chairman
M C Petch, Secretary
(Specialist Advisory Committee)

Br Heart J 1985; 53: 337–40

Case reports

A complicated case of mitral valve disease

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SUMMARY A patient with rheumatic mitral stenosis and previous cerebral embolism had a myocardial infarction during cardiac catheterisation. She later developed severe mitral regurgitation one year after open valvotomy and at valve replacement was found to have a papillary tumour of the mitral valve. Unexplained low cardiac output occurred four days after operation. Postmortem examination showed thrombotic occlusion of the xenograft prosthesis, a complication not previously seen with tissue valves. Both of these rare events were suggested by the patient's clinical course and could have been diagnosed with cross sectional echocardiography.

Symptoms of mitral stenosis may be identical to those of left atrial myxoma, and both lesions may coexist,[1] but the clinical importance of the more rare papillary tumour of the heart[2] and its relation to these two conditions is less well defined. In the present report, a mitral valve papillary tumour (or giant Lamdl's excrescence) may have caused many complications attributed to the patient's rheumatic mitral stenosis. In addition, the early postoperative occlusion of a xenograft prosthesis is reported.

Case report

A 57 year old woman was referred for cardiac assessment in November 1979. She had had rheumatic fever at 18 years of age, and three pregnancies were complicated by heart failure. Subsequently, only mild dyspnoea occurred on effort, but in 1977 she had a left cerebral embolus while in sinus rhythm.

Physical examination showed signs of predominant mitral stenosis with mild mitral and aortic regurgitation as well as a residual right hemiparesis. An electrocardiogram confirmed sinus rhythm and left atrial enlargement, while chest *x* ray films showed a dilated left atrium and upper lobe blood diversion. At cardiac catheterisation, there was a resting gradient of 10 mm Hg across the mitral valve and a pulmonary artery pressure of 50/24 mm Hg. Angiography detected slight mitral and aortic regurgitation, good left ventricular function, and normal coronary arteries. Several minutes after completion of the catheter study, the patient experienced chest pain and bradycardia. Changes of inferolateral ischaemia on the electrocardiogram evolved, and myocardial necrosis was confirmed by an increase in serum creatine phosphokinase activity from 74 to 1679 U/l. Review of events at catheterisation suggested no obvious cause for the myocardial infarction.

Six months later an open mitral valvotomy was performed and the left atrial appendage amputated. The valve was mobile, without calcification, and remained competent after the commissures were opened to a diameter of 4·5 cm. There was no clot in the left atrium, but the apex of the heart was thin and scarred, consistent with previous myocardial infarction. The patient's postoperative recovery was complicated by multiple episodes of ventricular tachycardia and fibrillation; but, eventually, she was discharged from hospital in sinus rhythm and without signs of heart failure.

The next 18 months saw gradual deterioration from progressive mitral and tricuspid regurgitation, which was made worse by the onset of atrial fibrillation. In addition to several admissions for ventricular and atrial arrhythmias, she required admission to hospital for pneumonia, pulmonary embolus, and eventually severe congestive heart failure. Reinvestigation in October 1981 showed moderate restenosis of the mitral valve, which was now severely regurgitant. The anterior leaflet appeared mobile on cross sectional

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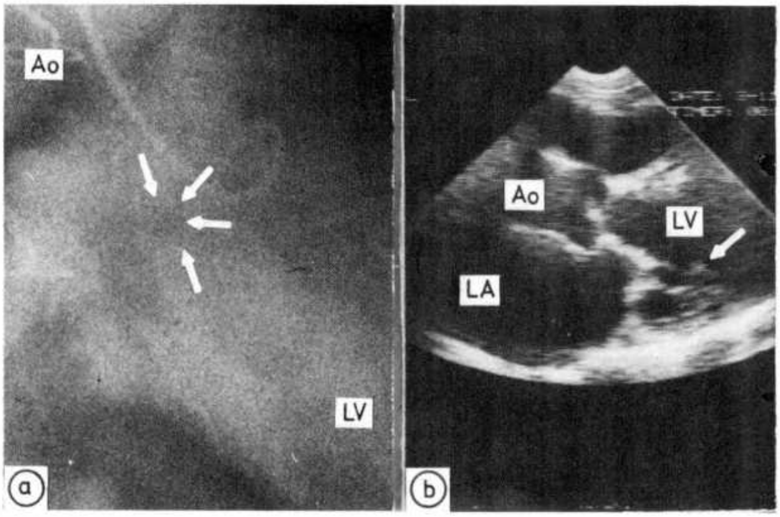

Fig. 1 *(a) Lateral view of left ventricular angiogram and (b) long axis view of echocardiogram showing the mass attached to the mitral papillary muscle (arrows). Ao, aorta; LV, left ventricle; LA, left atrium.*

echocardiography, but the posterior leaflet was rigid and the left atrium greatly enlarged (Fig. 1). Angiography showed anterior and apical akinesis of the left ventricle with abrupt occlusion of the posterior descending coronary artery. A thallium perfusion scan showed infarction of both the inferior wall and apex, consistent with involvement of two coronary arteries. A lung scan was now normal as were coagulation studies.

At a second open heart operation in March 1982, the mitral valve was replaced with a 25 mm Carpentier-Edwards xenograft using continuous 2/0 monofilament suture reinforced with a strip of Teflon felt along the posterior mitral annulus. Tricuspid regurgitation was repaired by a modified De-Vega annuloplasty. In addition to thickening of the mitral valve leaflets, a papillomatous jelly-like mass was found on the anterolateral papillary muscle (Fig. 2). Severe low cardiac output in the immediate postoperative period responded to isoprenaline, dopamine. Intermittent mandatory ventilation had and by the third postoperative day satisfactory haemodynamics were maintained with 5 μg/kg/min of dopamine. Intermittent mandatory ventilation had been reduced to 4 breaths/min with 40% inspired oxygen. Nevertheless, the following day the patient again developed insidious low cardiac output. Cardiac tamponade was excluded by resternotomy. Despite reinstitution of all supportive measures she died five days after operation.

At the coroner's postmortem examination, a large thrombus occupied nearly half of the left atrium and extended across the orifice of the xenograft prosthesis. The major coronary arteries were normal on gross examination. Histological examination of the mass removed at operation showed the characteristic features of a papillary tumour or giant Lamdl's excrescence. In retrospect, this could be identified on the preoperative echocardiogram and left ventricular angiogram (Fig. 1).

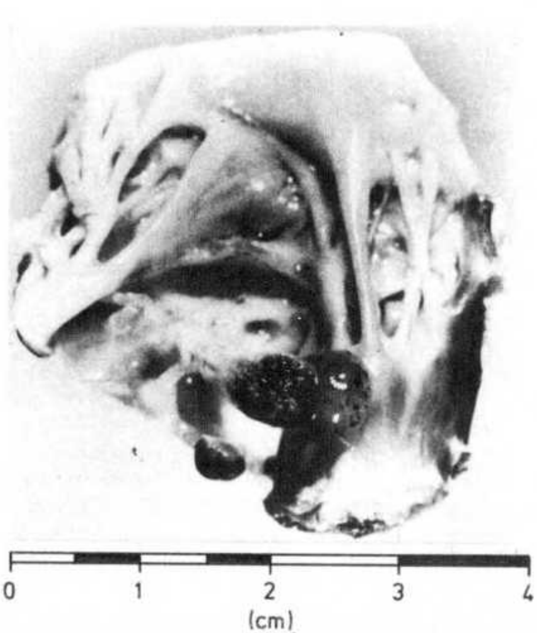

Fig. 2 *Morphological appearance of the mitral valve removed at the second operation. The tumour mass is attached to the anterolateral papillary muscle.*

Discussion

Primary cardiac tumours are rare, the commonest being myxomas and papillary tumours of the heart valves.[2] The latter generally have been incidental findings at postmortem examination or open heart surgery. Because of their predilection for the ventricular surface of the semilunar valves and atrial surface of the atrioventricular valves, as well as their histological similarity to Lamdl's excrescence, the papillary tumour has been thought to originate from mural thrombus.[3,4] Nevertheless, the ultrastructure and histochemistry are not unlike that of the atrial myxoma,[5] and both single and multiple tumours have been found within the left ventricle.[4,6,7]

While the aetiology and classification of the papillary tumour and giant Lamdl's excrescence remain controversial, this case and other recent observations indicate they may not be as harmless as previously believed. Prolapse into a sinus of Valsalva has obstructed the right coronary ostium, producing chest pain[8,9] and causing sudden death.[10] Coronary[7,11] and cerebral emboli[12] have been associated with such lesions and, in this case, occurred while the patient was in sinus rhythm, suggesting the possibility of a cardiac tumour.[13]

Like many of the reported cases, this left ventricular papillary tumour was found in a patient who had undergone previous valvotomy for rheumatic mitral stenosis.[6,7] Whether endocardial injury at the time of valvotomy provides a nidus for mural thrombus and subsequent papillary tumour formation or the rheumatic process is associated with these lesions is unknown. Alternatively, an undetected abnormality of haemostasis may have predisposed to both the formation of the papillary tumour and thrombosis of the mitral valve prosthesis.

While the risk of late degeneration in gluteraldehyde-preserved porcine bioprostheses is recognised, low thrombogenicity has made them an attractive alternative to mechanical devices for cardiac valve replacement. The reported incidence of thromboembolic episodes with the Carpentier-Edwards and other mitral xenograft valves ranges from 0%[14,15] to about 11% per patient per year,[16] depending, in some series, on the patient population and the use of anticoagulation or antiplatelet treatment. Rarely, thrombotic stenosis has developed in xenograft valves implanted for longer than one month.[17] This was manifest by systemic emboli,[18] prosthetic occlusion,[19] or signs of prosthetic valve stenosis.[20] Such valves had acute or organising thrombus in one or more cusps, thought to be the result of primary thrombogenicity of the valve tissue,[17] infection,[19] or impaired cusp mobility from muscle,[21] degeneration,[11,19] or haematoma.[22]

In contrast to late thrombotic complications, early thrombus formation does not appear to be related to the heterograft tissue. An incidental finding in four of 32 Hancock valves removed within one month of insertion,[17] the clot was attached to the prosthetic sewing ring or left atrium and in no case obstructed the valve orifice. Factors predisposing to early thrombus formation were postoperative low cardiac output, atrial fibrillation, a Dacron sewing ring in the left atrium, and absence of anticoagulation.[17,20,23]

All of these factors were present in our patient, who developed much more extensive thrombosis than previously observed with a xenograft prosthesis. In addition, the strip of Teflon felt used to reinforce the mitral annulus in the left atrium may have contributed to clot formation, which almost certainly resulted in recurrence of low cardiac output by progressive occlusion of the prosthetic orifice. Had this complication been suspected, it could have been diagnosed by echocardiography and possibly treated by streptokinase infusion or surgical removal. Recognition of such a patient at risk of early valve thrombosis would be a clear indication for anticoagulation in the early postoperative period.

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Mitral obstruction in bacterial endocarditis

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SUMMARY Mitral obstruction due to a large vegetation of acute *Streptococcus viridans* endocarditis occurred in a 47 year old man. Serial echocardiography documented the rapid growth of the vegetation and its haemodynamic effects. Emergency mitral valve replacement was performed too late to reverse the course of fatal septic shock.

Bacterial endocarditis of the mitral valve usually results in mitral regurgitation.[1 2] Since 1967 we have been able to trace only seven cases of mitral obstruction as a complication of infective endocarditis in English language reports.[3–9] We report the preoperative diagnosis and the surgical management of this rare and lethal lesion.

Case report

A 47 year old man was admitted to hospital with a pyrexia of 39°C, with chill and rigor, nausea, anorexia, and dysuria for two weeks. His symptoms had started 24 hours after extraction of a tooth. He had treated himself with dipyrone tablets only. His hypersensitivity to penicillins was recognised six years ago when he was operated on for a lumbar disc lesion. He had no history of rheumatic fever.

Physical examination on admission showed cachexia, a blood pressure of 130/80 mm Hg, and sinus tachycardia of 130 beats/minute. A grade 3/6 diastolic rumble and a grade 1/6 systolic murmur were heard at the apex. The chest radiograph showed mild cardiomegaly with prominence of the right border of the heart. The electrocardiogram confirmed sinus tachycardia with normal axis. There was polymorphonuclear neutrophilic leucocytosis with a total white cell count of $12{\cdot}0\times10^9$/l. Urine analysis showed 1–2 white cells and occasional red cells per high power field, and the sample was sterile on culture. Blood cultures were also sterile. An echocardiogram (Fig. 1) showed a mildly stenotic thickened mitral valve with minimal regurgitation and an enlarged left atrium. No valvar or atrial vegetation was seen.

He was initially treated for urinary tract infection with gentamycin, which controlled the fever. An intravenous pyelogram did not provide any additional information. Three weeks later he developed atrial fibrillation, when a second echocardiogram was recorded. It showed severe mitral obstruction with minimal regurgitation due to a huge echogenic mass 2 cm × 4 cm in size, which nearly occluded the mitral orifice. The aortic valve was normal. The left ventricle was of normal size and contracted well (Fig. 1). Blood cultures at this stage grew *Streptococcus viridans*. The patient developed congestive heart failure. Conservative treatment with vancomycin, digoxin, quinidine, and frusemide for bacterial endocarditis and cardiac failure was started in view of his critical clinical condition. Nevertheless, he did not respond to medical management and gradually became hypotensive and required intubation and mechanical ventilation. Ten days later he was referred for cardiac surgery in a state of septic shock.

At operation a large pericardial effusion was noted and 4000 ml of straw coloured fluid was drained off both pleurae. The heart was enlarged with a very tense main pulmonary artery. A large greyish brown vegetation 2 cm × 4 cm in size was arising from the anterior mitral leaflet and the adjacent left atrial wall near the anterolateral commissure and almost occluded the mitral orifice (Fig. 2). It was removed, and the valve was replaced with a size 31 Björk-Shiley prosthesis. Postoperatively, the septic shock remained uncontrollable despite all measures, and pulmonary hypertension contined at 52/35 mm Hg. Renal failure supervened from the second postoperative day, and he died of septic shock on the fifth day.

Discussion

Mitral obstruction complicating bacterial endocarditis

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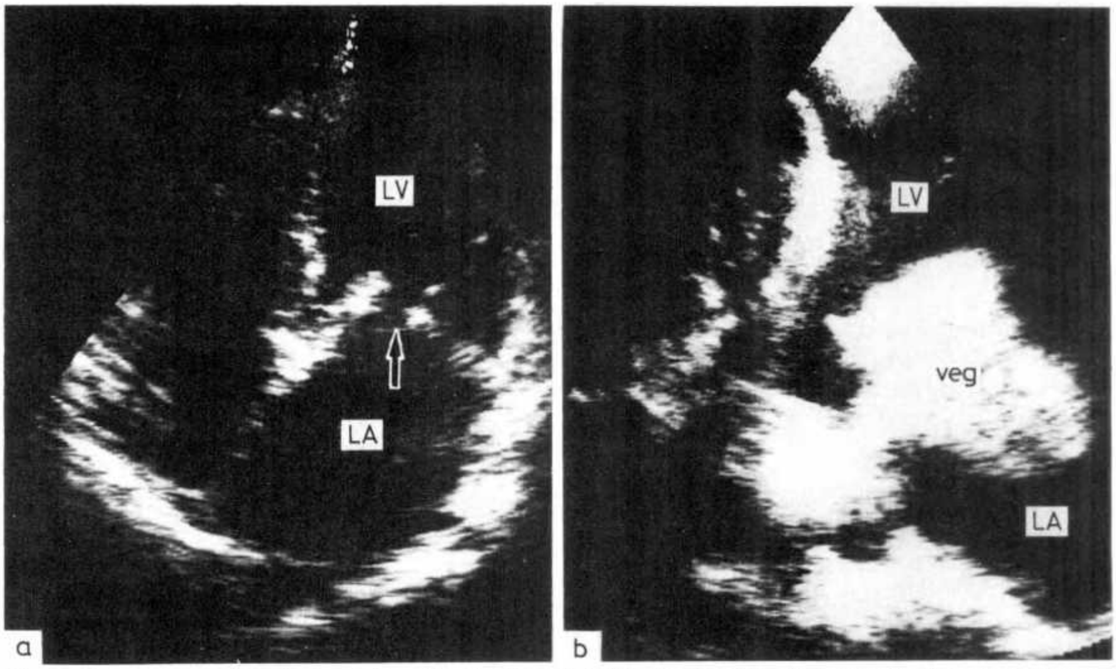

Fig. 1 *Cross sectional echocardiograms (a) in a four chamber apical view showing enlarged left atrium (LA) and thickened mitral leaflets (arrow). No vegetation can be seen. Left ventricle (LV) is of normal size; (b) in a modified four chamber apical view three weeks later showing a huge vegetation (veg) occluding the mitral orifice and extending into both the LA and LV.*

is very rare and mortality is high. If this case is added to the seven reported cases already mentioned only three of eight (37·5%) patients have survived (Table). Of these eight, five underwent mitral valve replacement. The three survivors[5 6 8] were operated on promptly after the diagnosis of endocarditic mitral obstruction had been made by echocardiography or cardiac catheterisation or both. Among the non-survivors one patient[7] was operated on in a rapidly deteriorating haemodynamic state and with congestive failure. He died seven days later from septic shock and a cerebrovascular accident. Our patient was similarly referred in a moribund state to surgery after 30 days in hospital and too long a trial of conservative management. He too succumbed to septic shock five days after the operation. Of the three other reported cases, one was a necropsy finding in a patient who died four months after a normal delivery from a full-term pregnancy.[3] The other two who were treated conservatively had a very rapid downhill course and died after 10 and eight days respectively.[4 9]

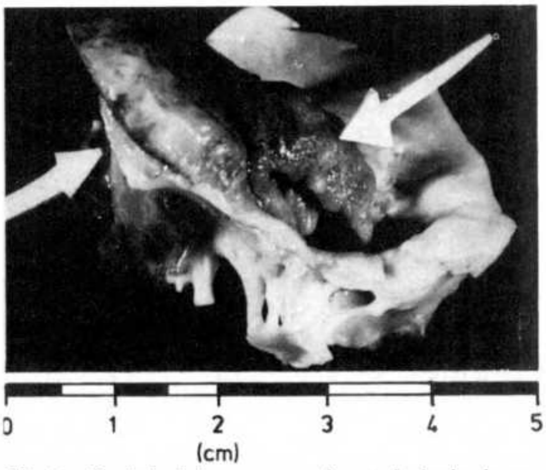

Fig. 2 *Morphological appearance of resected mitral valve seen from above showing huge mass arising from anterior mitral leaflet and left atrial wall at anterolateral commissure and nearly occluding mitral orifice (arrows).*

Cerebrovascular events occurred in four patients,[3 5-7] possibly due to embolism. In another patient, who died in coma and renal failure, at necropsy bacterial vegetations were also noticed beneath all three aortic cusps.

Echocardiography is important for prompt, accurate, early diagnosis[10 11] since emergency mitral valve replacement early in the clinical course may become mandatory. It may detect vegetations as small as 2 mm in diameter. Bacterial vegetations mimicking mitral stenosis have been found.[12] In an M mode echocardiogram the posterior mitral leaflet is difficult to differentiate from an echogenic mass obstructing the mitral orifice in later diastole. Nevertheless, dense echoes occurring soon after mitral valve opening would indicate an obstructing echogenic mass rather than valvar mitral stenosis. Left atrial myxoma may also resemble this lesion, but then there will be a mass of echoes from the body of the left atrium continuous with the atrial septum in the cross sectional echocardiogram. A sterile left atrial thrombus is difficult to differentiate by echocardiography from an obstructing vegetation due to mitral endocarditis, but the clinical picture of the latter should help in diagnosis. Our serial study is unique in showing rapid growth of a vegetation so that in three weeks it became a giant mass which occluded the mitral orifice. This finding has not been previously reported. The cross sectional echocardiographic evidence was diagnostic and correlated with the operative findings. Nevertheless, contrary to our finding, Sheikh *et al* reported little or no change in the echocardiographic size of vegetations in 27 patients over a period of six weeks unless systemic embolisation occurred.[13]

Two types of vegetations are found in the mitral valve: (*a*) a globular or elongated mass as seen in five cases and (*b*) multiple verrucae occluding the mitral orifice as seen in two. The vegetations showed no predilection for site in the mitral apparatus. The posterior leaflet was the site in two patients, whereas the anterior leaflet was the primary area in three cases. The site of the vegetation was not mentioned in two cases. Signs of earlier rheumatic disease were noted in six.

In conclusion, mitral obstruction due to bacterial endocarditis is a dangerous complication with a rapidly deteriorating course often causing cerebrovascular accidents. Prompt diagnosis with M mode and cross sectional echocardiography alone should lead to emergency mitral valve replacement. Mitral valve replacement in bacterial endocarditis has usually been advocated in congestive heart failure due to mitral regurgitation or systemic embolisation.[14] We consider that the documentation of the rare possibility of mitral obstruction by vegetations should also indicate valve replacement early in the clinical course. Cardiac catheterisation is unnecessary,[11] and may increase the risk of embolism. Delayed surgical intervention may not be adequate to reverse the course of fatal septic shock.

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Table *Previously reported cases of mitral obstruction in bacterial endocarditis*

Author and year	*Age/sex*	*Signs of rheumatic disease*	*Echocardiography or cardiac catheterisation or both*	*Surgery/necropsy findings*	*Organism*	*Treatment*	*Result*
Roberts *et al*[3] 1967	21/F	Present	Not done	Vegetations from LA filled MV orifice	β Haemolytic streptococcus		Died after 1 mnth
Reeve *et al*[4] 1974	36/M	Present	Not done	Multiple vegetations on AML, aortic cusps involved	*Staphylococcus aureus*	Medical	Died after 10 days
Matula *et al*[5] 1975	51/M	Present	Multiple dense mitral echoes; EF slope less than 10 mm/s; RV enlarged; catheterisation confirmed MS; severe PH	A large vegetation occluding MV orifice	*Staphylococcus aureus*	MVR (porcine xenograft)	Survived
Copeland *et al*[6] 1979	52/F	Present	Decreased motion of AML; multiple adjacent echoes from LA aspect of AML; catheterisation confirmed MS	Multiple obstructive vegetations, each 2 mm ×3 mm; MV orifice 1·5 cm^2	Negative	MVR (porcine xenograft)	Survived
Alam *et al*[7] 1979	65/F	Absent	Reduced EF slope; increased mass of echoes in latter 3/4 of diastole behind AML; CSE showed obstructing mass in diastole adherent to MV in systole; no fibrous continuity with septum	Soft brownish globular mass from PML, 4 cm in diameter	β Haemolytic streptococcus	MVR (porcine xenograft)	Died after 7 days from CVA, septic shock
Waller *et al*[8] 1982	37/M	Present	Typical MS in M mode echo; catheterisation showed mean diastolic mitral gradient of 26 mm Hg		*Staphylococcus aureus*	MVR	Survived
Grenadier *et al*[9] 1983	40/M	Absent	Huge mass 3·5 cm×4 cm from PML in CS and M mode echoes	Giant globular mass from PML; several abscesses in myocardium	*Staphylococcus aureus*	Medical	Died suddenly after 8 days
Ghosh *et al* (present report) 1985	42/M	Present	Huge mass 3 cm×4 cm occluding MV; minimal MR on Doppler sampling; serial documentation of growth of mass over 3 week period	Brown large mass 2 cm×4 cm from AML and LA wall at ALC	*Streptococcus viridans*	MVR (Björk-Shiley prosthesis)	Died after 5 days from septic shock

MV, mitral valve; AML, anterior mitral leaflet; LA, left atrium; PML, posterior mitral leaflet; RV, right ventricle, MVR, mitral valve replacement; CSE, cross sectional echocardiography; MR, mitral regurgitation; MS, mitral stenosis; ALC, anterolateral commissure; PH, pulmonary hypertension.

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Verapamil in primary pulmonary hypertension

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SUMMARY An 8 year old girl with primary pulmonary hypertension and signs of heart failure was given 17·5 mg of verapamil injected into the pulmonary artery over 25 minutes to test for the reversibility of pulmonary arteriolar obstruction. Pulmonary artery pressure fell from 70/50 to 35/25 mm Hg. Treatment with 40 mg verapamil by mouth four times daily was started, and she was discharged. She gradually became asymptomatic and resumed the activities of a normal child of school age. On recatheterisation seven months later her pulmonary artery pressure was 30/10 mm Hg. She was still doing well 12 months after the start of treatment.

Primary pulmonary hypertension has a poor prognosis and is a frustrating problem for the managing physician. Calcium antagonists have smooth muscle relaxing properties[1] and well known systemic vasodilator and antihypertensive effects.[2] McMurtry *et al* showed on a rat lung model that calcium antagonists were capable of inhibiting the hypoxic pulmonary vasoconstriction response.[3] Patients with primary pulmonary hypertension have subsequently been treated with these agents with varying degrees of success.

Case report

An 8 year old girl was admitted for investigation of palpitation, chest pain, progressive breathlessness, and fatigue. The symptoms had appeared and worsened during the preceding year. On examination she was slightly tachypnoeic and cyanotic. Her weight was 27·4 kg, height 137 cm. There was a left precordial lift and a clearly palpable second heart sound over the base of the heart. A grade 2/6 mid systolic murmur, an early diastolic murmur, and the booming and split second heart sound could be heard in the pulmonary area. Radiographs indicated an enlarged heart shadow with prominent proximal pulmonary vascular markings tapering sharply in the periphery. Electrocardiography (Fig. 1) showed right axis deviation (+130°), right atrial and right ventricular hypertrophy, and the right ventricular strain pattern. Echocardiography showed evidence of an enlarged (2 cm) and highly trabeculated right ventricle, thickening of the interventricular septum (1·5 cm), and a dilated right ventricular outflow tract. The two branches of the main pulmonary artery were widened; the right one appeared to be wider than the aorta. The pulmonary valve produced a very shallow "a" wave, a partial systolic closure, and a horizontal diastolic echo movement. Radiocardiography did not show any signs of intracardiac shunting. The liver was palpable 3 cm below the right costal margin. The neck veins were distended. We could not elicit a history suggesting any kind of peripheral thrombosis or pulmonary thromboembolism.

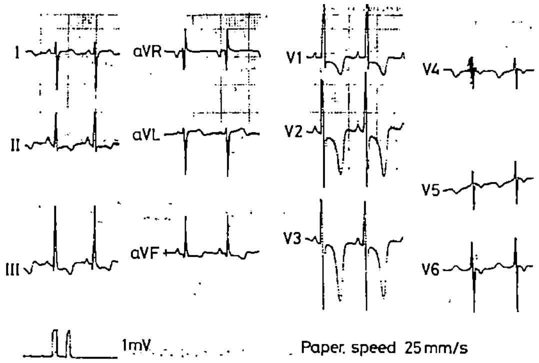

Fig. 1 *Electrocardiograms before treatment. The tall and peaked P wave in leads II and V2 is characteristic of right atrial enlargement. The electrical axis is deviated to the right. The signs of right ventricular hypertrophy are accompanied by inverted and deep T waves in V2 and V3 and ST segment depression in V1 to V3 indicating right ventricular strain.*

During catheterisation she had raised right ventricular and pulmonary artery pressures. The mean

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Table *Haemodynamic data obtained at catheterisation before treatment and immediately after injecting verapamil into the pulmonary artery and at recatheterisation after seven months' oral treatment with verapamil*

	Before treatment	*Immediately after injection of verapamil*	*After seven months' oral verapamil*
Pulmonary artery pressure (mm Hg)	70/50	35/25	30/10
Pulmonary vascular resistance (dyn s cm^{-5})	607·9	364·7	226·4
Cardiac index (l/min per m^2)	3·29	3·29	4·42
Mean right atrial pressure (mm Hg)	8		4
Right ventricular systolic/end diastolic pressure (mm Hg)	55/10	40/10	25/0
Heart rate (beats/min)	110	70	80
Systemic blood pressure (mm Hg)	110/65	95/60	100/60

Conversion—kPa = mm Hg/7·5.

pulmonary artery wedge pressure was 15 mm Hg (2 kPa). A total of 17·5 mg verapamil was given over 25 minutes (2·5, 2·5, 2·5, 5·0, and 5·0 mg at five minute intervals) into the pulmonary artery with prompt improvement in the haemodynamic indices (Table).

After catheterisation she was given 40 mg verapamil by mouth four times daily. Over the next few months she became asymptomatic and resumed her normal activities, which included walking 7 km daily. Seven months later she was admitted for recatheterisation. She had no subjective symptoms, cyanosis, or precordial lift, and the second heart sound was no longer palpable. The diastolic murmur had disappeared, the systolic murmur was of grade 1/6, and the second heart sound was slightly accentuated. Radiographs showed the heart shadow to be of normal size, the pulmonary artery to be slightly prominent, and peripheral pulmonary vascular markings to be normal. The electrocardiogram did not show any evidence of right atrial hypertrophy or right ventricular strain pattern, the heart axis was +95°, and the right ventricular hypertrophy was appreciably improved (Fig. 2). Residual echocardiographic abnormalities included an enlarged right ventricle, dilated pulmonary artery branches, and thickening of the interventricular septum. The liver was not palpable below the costal margin. The Table shows the pressures and haemodynamic values obtained on recatheterisation.

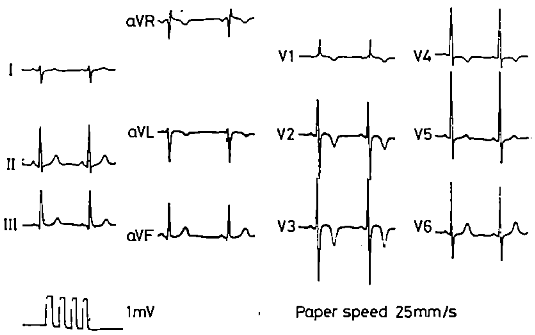

Fig. 2 *Electrocardiograms after seven months' treatment with verapamil. The P wave is now normal and the electrical axis nearly vertical. Signs of right ventricular hypertrophy have improved, and the ST segment has returned to the baseline indicating the disappearance of the right ventricular strain.*

The dose of verapamil was changed to 60 mg by mouth three times daily, and she was discharged. Twelve months after the start of the treatment she was still undergoing regular check ups and was doing well clinically, according to electrocardiographic and radiographic findings. No untoward side effects of the drug were seen throughout the treatment.

Discussion

Our patient presented with a typical picture of comparatively rapidly developing primary pulmonary hypertension. Her pulmonary artery pressure and pulmonary vascular resistance were noticeably increased. The cardiac index was not, however, appreciably depressed. This feature may be seen in early primary pulmonary hypertension and has been found in other patients.[4] On administering verapamil into the pulmonary artery we observed prompt haemodynamic improvement which was sustained throughout long term oral treatment. On recatheterisation her cardiac index was increased and the pulmonary artery pressure and pulmonary vascular resistance were virtually normal.

One young woman has been reported to have experienced similar clinical and haemodynamic improvement when treated with nifedipine, another calcium blocking agent.[4] She was followed up for six months. Two other young women have been reported to have gained appreciable clinical benefit from treatment with nifedipine.[5 6] The fall in their respective pulmonary artery pressures was not, however, impressive, and the pulmonary vascular resistances remained above expected normal values. Their cardiac outputs were also increased. They were followed up for three and four months respectively. Similar clinical and haemodynamic effects have been reported in a young woman treated with diltiazem and followed up for 11 months.[7]

Another young woman has been reported to have had a precipitous fall in pulmonary artery pressure after 20 mg nifedipine, but the effect could not be sustained for longer than three hours despite the administration of additional nifedipine.[8] Farber *et al* reported death 54 hours after starting nifedipine in a 63 year old man with pulmonary hypertension secondary to a long standing sarcoidosis but could not relate it clearly to the drug.[9]

It is not clear why certain patients with primary pulmonary hypertension show remarkable improvement when treated with calcium blocking agents while others improve less or not at all. The one obvious prerequisite for success is the absence of the fixed anatomical obstruction of the pulmonary arterioles. Some authors claim that the improvement is consequent on increased cardiac output rather than on a decrease in pulmonary artery pressure, which in certain patients is only modest.[10] Until we obtain reliable data from controlled clinical trials all individual cases must be reported thoroughly, both successes and failures, to define more factors that might influence the chances of successful treatment.

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Br Heart J 1985; 53: 348

William Withering commemoration meeting

A symposium, organised jointly by the Association of Physicians and British Cardiac Society, to commemorate the bicentenary of the publication of William Withering's *An Account of the Foxglove* is to be held on 18 April 1985 in the Haworth Lecture Theatre, Chemistry Building, University of Birmingham. Space for non-members of the British Cardiac Society is limited and inquiries should be made to: Professor W A Littler, Department of Cardiovascular Medicine, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST.

Programme

9.30 am	Registration in foyer; coffee upstairs
10.00 am	SESSION 1—Chairman: M F Oliver Pharmacology of digoxin—T W Smith (Brigham and Women's Hospital, Boston, USA) *(Strickland-Goodall Lecture)* Modern views of myocardial contractility—S V Perry (Department of Biochemistry, University of Birmingham) Digitalis and membranes—Denis Noble (Department of Physiology, University of Oxford)
11.30–12.00 noon	Coffee in the University Centre
12.00 noon	SESSION 2—Chairman: Sir Melville Arnott Digitalis for arrhythmias—D M Krikler (Royal Postgraduate Medical School, London) Digitalis toxicity—Charles Fisch (Indiana University School of Medicine, USA)
1.00–2.30 pm	Lunch in the University Centre
2.30 pm	SESSION 3 *"Should we be using digitalis?"*—A debate *Chairman*—H B Burchell (Saint Paul, Minnesota, USA) *For*—W A Littler (Birmingham) F L Meijler (Utrecht) *Against*—A Guz (London) D G Gibson (London)
4.00–4.30 pm	Tea in the University Centre
5.00 pm	SESSION 4 *The Royal College of Physicians William Withering Lecture*—Chairman: Sir Raymond Hoffenberg, PRCP The current treatment of heart failure—C T Dollery (Royal Postgraduate Medical School, London)
	SOCIAL EVENTS
6.30 pm	Visit to Edgbaston Parish Church for the Commemoration and concert by the English String Orchestra Historical address—A G W Whitfield
7.45 pm	Reception at Edgbaston Hall

Br Heart J 1985; **53:** 349–52

Correspondence

Lead specificity of the maximum ST/heart rate slope response

Sir,

We read with interest the paper by Balcon *et al* (1984; 52: 304–7) describing a relatively poor correlation between the maximum ST/heart rate slope and the severity of coronary artery disease at angiography. While this and most studies to date have been based on the derivation of this variable from conventional 12 lead electrocardiographic systems with an additional precordial electrode, CM5, we have recently obtained similar results with a computerised Frank orthogonal lead system.[1] In 98 men studied by upright bicycle ergometry and coronary angiography, the maximum rate of change of ST amplitude was a poor predictor of the extent of coronary artery disease. Although a broad relation existed between the magnitude of this variable and the number of significantly diseased vessels, defined as >75% luminal stenosis, the degree of overlap was such that accurate discrimination of vessel disease groups was not achieved.

Advocates of the use of the maximum ST/heart rate slope as an index of severity of coronary atherosclerosis suggest that the slope may be selected from any lead in which the linear regression of ST change on heart rate is significant. This assumes that the ST response to exercise is uniform in all leads and that a common pathophysiological mechanism—namely, a mismatch of myocardial oxygen supply and demand—is the sole determinant of such a response. Using the Frank lead system we have found that these assumptions are invalid and that responses are lead specific.[2] Maximum rates of change of ST amplitude are similar in leads X and Z but greater in lead Y. It is likely that this disparate response is due to a disproportionate effect of exercise induced augmentation of the atrial repolarisation (Ta) wave on the early part of the ST segment in vertically orientated leads.[3]

This non-uniformity in lead response is evident in the data presented by Balcon *et al,* who documented the lead from which the maximum ST/heart rate slope was sampled in 27 patients, 19 of whom had single vessel disease. This vessel disease group comprised eight patients with right coronary artery and 11 with left anterior descending disease. Although dominance of the coronary circulation is not reported, precluding estimation of the amount of jeopardised myocardium subtended in each patient, we may assume that this subpopulation is homogeneous, and as such maximum ST/heart rate slopes should be comparable. It is clear, however, that slopes sampled from leads II, III, and aVF, which are predominantly vertically orientated, tend to be of greater magnitude (mean 41) than those from lateral leads I, aVL, V4–6 (mean 31). Slopes selected from CM5 which has both vertical and horizontal components are even greater (mean 48) suggesting the influence of additional confounding variables.

The relative contributions of normal physiological responses and underlying pathology as determinants of the maximum ST/heart rate slope appear to be lead dependent, and the development of lead specific criteria for normal and abnormal ST/heart rate slope responses may improve diagnostic accuracy and facilitate the development of a multivariate model for better assessment of overall myocardial ischaemia.

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Pathways of preferential atrial conduction

Sir,

We read with both interest and concern the account of Dr T N James (1984; **52:** 1–23) concerning the debate on the anatomical substrates for internodal conduction. From his review, we draw the inference that he believes the issue to have been clouded by workers such as ourselves.[1] This is because, following the precedent set at a meeting of the German Pathological Society in 1910,[2] we have suggested that the model for an anatomically discrete conduction system should be the insulated series of tracts found within the ventricular myocardium. In raising this matter, Dr James must be aware that, after his own initial paper,[3] some distinguished cardiologists[4] came to accept that such a system of tracts did exist within the atrial myocardium. Furthermore, these "tracts" have been illustrated in books prepared for "general consumption"[5-7] in a fashion analogous to the ventricular bundle branches. As Dr James knows well, there is no anatomical evidence for the existence of such insulated tracts in the atrial tissues. It is significant in this respect that his own diagrams of the pathways have changed from the single solid lines of his 1963 drawing[3] to the more vague discontinuous lines of his present figure (Fig. 4, p.5). Yet even now we are unaware of any anatomical evidence that shows that the atrial myocardium in the areas he illustrates as "pathways" is any different morphologically and histologically from that elsewhere in the atrial wall and septum. This is particularly so in the case of his "middle pathway," which seems to pass directly through the site of the oval fossa. Dr James accuses us of raising a straw man when we discuss the specialisation of the atrial myocardium. We plead not guilty to this charge. But is he not guilty of this offence when he raises the matter of the structure of the sinus node? The sinus node is primarily designed to generate the impulse. Although its cells must then also conduct, they do not have conduction as a primary function, as do the ventricular bundle branches. He goes on to construct another straw man when he argues that these ventricular bundle branches themselves are composed of several cell types. Here, and elsewhere, he misses the whole point of our argument. Irrespective of their cellular composition, the ventricular bundle branches can be traced through serial histological sections because they are insulated from the ventricular myocardium. If the tissue within the insulating sheaths is divided conduction into the ventricles ceases. This is certainly not the case with the atrial myocardium. Dr James then raises a third straw man concerning the specialised action potentials of atrial cells. There is no doubt that there are several populations of cells in the atrial tissues that have different action potential configurations. There is also evidence that "sinoventricular conduction" can occur when the atrial myocardial cells themselves are paralysed. But we know of no evidence that has shown that those cells with specialised potentials conduct any more rapidly than the "working" cells nor that an anatomically discrete system of atrial cells is responsible for sinoventricular conduction. The only paper of which we are aware that investigated the morphology of these cells showed that both specialised and working potentials originated from areas of plain atrial myocardium.[8] Furthermore, as Dr James himself states, the recent work of Spach and his colleagues[9] has shown that the simple geometry of the atrial septum accounts fully for preferential conduction between the nodes. If, Sir, the histological appearance and constituents of the atrial cells also are involved in this process of preferential conduction, it is incumbent upon Dr James to produce the evidence supporting this rather than obfuscating the topic still further with skilful rhetoric.

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This letter was shown to the author, who replies as follows:

Sir,

Thank you for the privilege of responding to the letter from Drs Anderson and Becker. Much of their concern now and in the past has to do with the purported insulation of the internodal pathways, but it is unclear why they address their criticisms to me. As they very well know, I have never said or written that these pathways are shielded or insulated in any way. The reason my original drawing which showed solid lines has been changed to one with interrupted dashes (Fig. 4, p 5) (which I do not believe are "vague") is to encourage others not to misinterpret this matter. Drs Anderson and Becker indicate that they are unaware of anatomical evidence that the atrial myocardium in the internodal pathways is different, choosing to ignore Figs. 5 and 6 (p 6 and 7) as well as the work cited in my references 27, 31, 33, 39, 40, 43, 44, 55, and 62 (p 20 and 21). Cardiac anatomists as experienced as Maurice Lev and Lino Rossi find no difficulty in identifying the preferential internodal pathways. Drs Anderson and Becker suggest that the middle internodal pathway appears to pass through the fossa ovalis, but my original description and that of all other subsequent investigators (for example, see Figs. 8, 9, and 10 in reference 4 cited by them) have explained how it combines with the descending portion of the anterior internodal pathway within the torus Loweri, which forms the anterior margin of the fossa ovalis. They accuse me of missing their point, when I emphasise that the bundle branches include more than one cell type, but what the latter fact indicates is that we have a long way to go in understanding the precise function of any of the wide variety of cells present in the myocardium, including the bundle branches. Their comment that the bundle branches can be traced in serial sections is true only for their proximal portion. No one to my knowledge has been able to trace much more than the first 20 or 30 mm of the course of the human left bundle branch nor of the right branch once it leaves the moderator band. They say that division of a bundle branch causes conduction into the ventricles to cease, which is simply not true. One can divide the right branch experimentally or demonstrate its complete interruption by disease in man, but the right ventricle still becomes activated, although about 20 ms more slowly. Evaluating either experimental or postmortem evidence of the effects from division of the left bundle branch is considerably more difficult, as Lenegre and others long ago demonstrated, but it is probable that complete interruption of it is still associated with activation (20 or 30 ms delayed) of the left ventricle. Following their erroneous statement that interrupting a bundle branch would terminate conduction to the ventricle, they say "this is certainly not the case with the atrial myocardium." But observations cited in my references 23, 32, 35, 37, 39, 53, 57, and 64–66 (p 20 and 21) offer evidence to the contrary: interruption of these pathways does delay atrial conduction. In referring to the work of Spach and his colleagues (my reference 58) I did not write that geometric histology fully accounts for preferential conduction but that it was a valid component of that explanation. Both older research (my references 51, 52, 60, and 61) as well as that more recent (59, 72, and 73) support the concept of preferential conduction via internodal pathways in the atria, including its participation in atrial flutter. Thus, Sir, it is the evidence which Drs Anderson and Becker choose to ignore which may be the explanation of why they continue to find the topic obfuscating.

Thomas N James,
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University of Alabama Medical Center,
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Left ventricular platelet deposition after acute myocardial infarction

Sir,
Verheugt and colleagues (1984; **52**: 490–6) have made a solid new addition to the many previously reported differences[1] between Q wave and non-Q wave myocardial infarction: the selective tendency for left ventricular thrombosis in the former. Since the presence of a Q wave cannot reliably distinguish anatomically transmural from non-transmural infarction[1 2] it is unfortunate that the authors have continued the standard, but erroneous labelling. (It may well be that the majority of Q wave infarcts are indeed anatomically transmural and many of the non-Q wave infarcts non-transmural, but the electrocardiogram is not able to distinguish these with certainty.)

This would be a terminological quibble if it were not that mislabelling can cloud concepts. By avoiding the inaccurate label perhaps further efforts will be directed at distinguishing further real, and it is to be hoped, fundamental differences between Q wave and non-Q wave infarcts.

David H Spodick,
Division of Cardiology,
St Vincent Hospital,
Worcester, Massachusetts, USA.

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Notices

Body surface mapping

The 3rd International Symposium on body surface mapping will be held from 11 to 14 June 1985 at the University of Nijmegen, The Netherlands. Further information may be obtained from: Dr R Th van Dam, Department of Cardiology, Geert Grooteplein Zuid 8, 6525 AG Nijmegen, The Netherlands.

British Cardiac Society

The Annual General Meeting for 1985 will take place in Birmingham on 17 and 18 April 1985, and the closing date for receipt of abstracts was 8 January 1985.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.

Unstable angina revisited

A clinical review of unstable angina organised by the Thoraxcenter, Erasmus University, Rotterdam, the Interuniversitary Cardiological Institute, Utrecht, The Netherlands, and the Toronto General Hospital, Toronto, Canada, is to be held in Rotterdam from 23 to 25 May 1985. Further details may be obtained from: Professor P G Hugenholtz, Thoraxcenter Bd 406, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

Non-invasive cardiovascular dynamics

The XIII European congress organised by the European Society for non-invasive cardiovascular dynamics will be held in Brescia, Italy, from 22 to 25 April 1985. Further details may be obtained from: Dr G Orlando, St Orsola Hospital, Via Vittorio Emanuele 27, 25122 Brescia, Italy.

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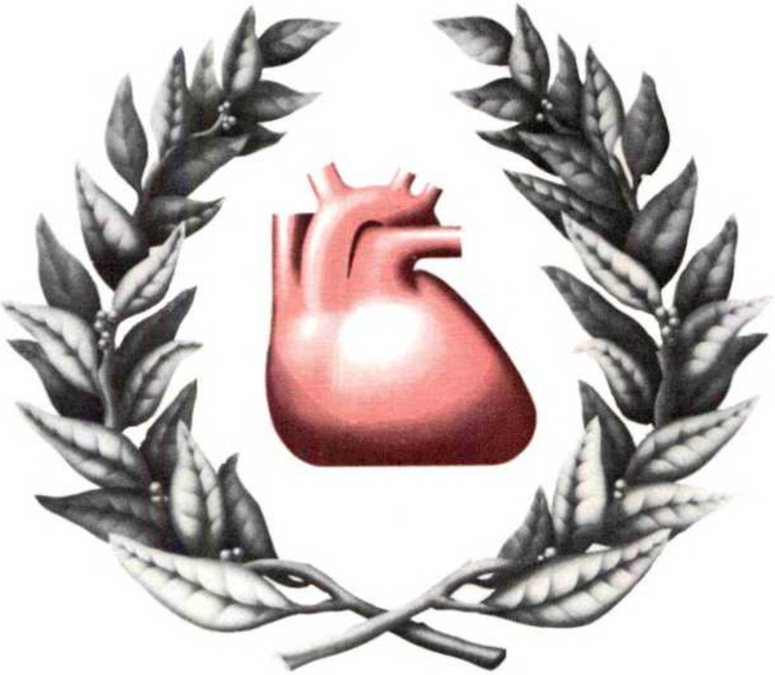

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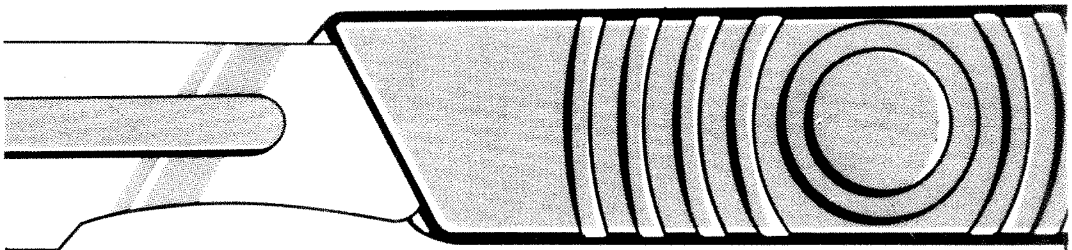

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British Heart Journal

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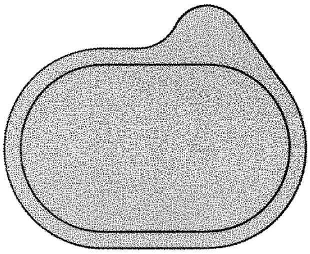

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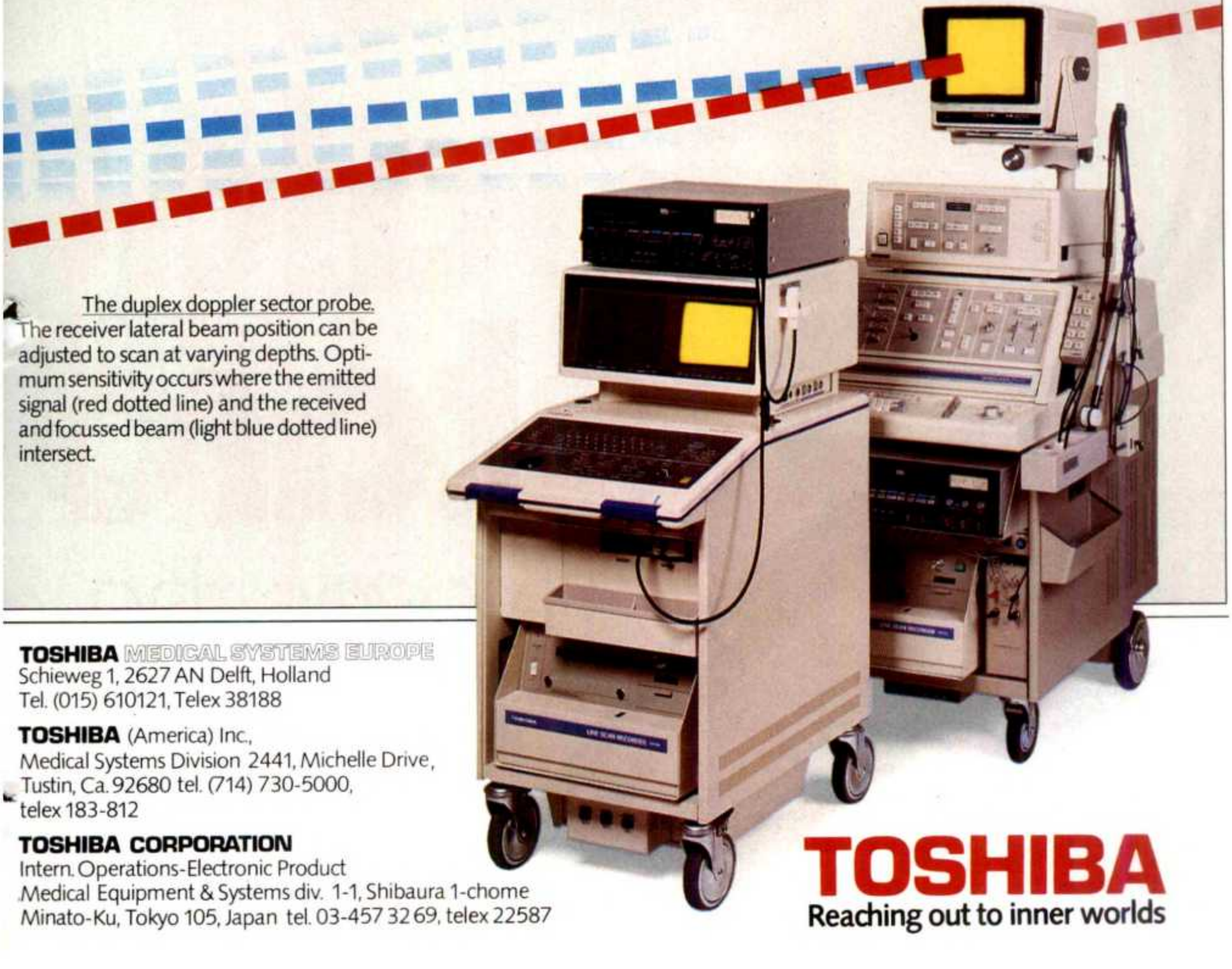

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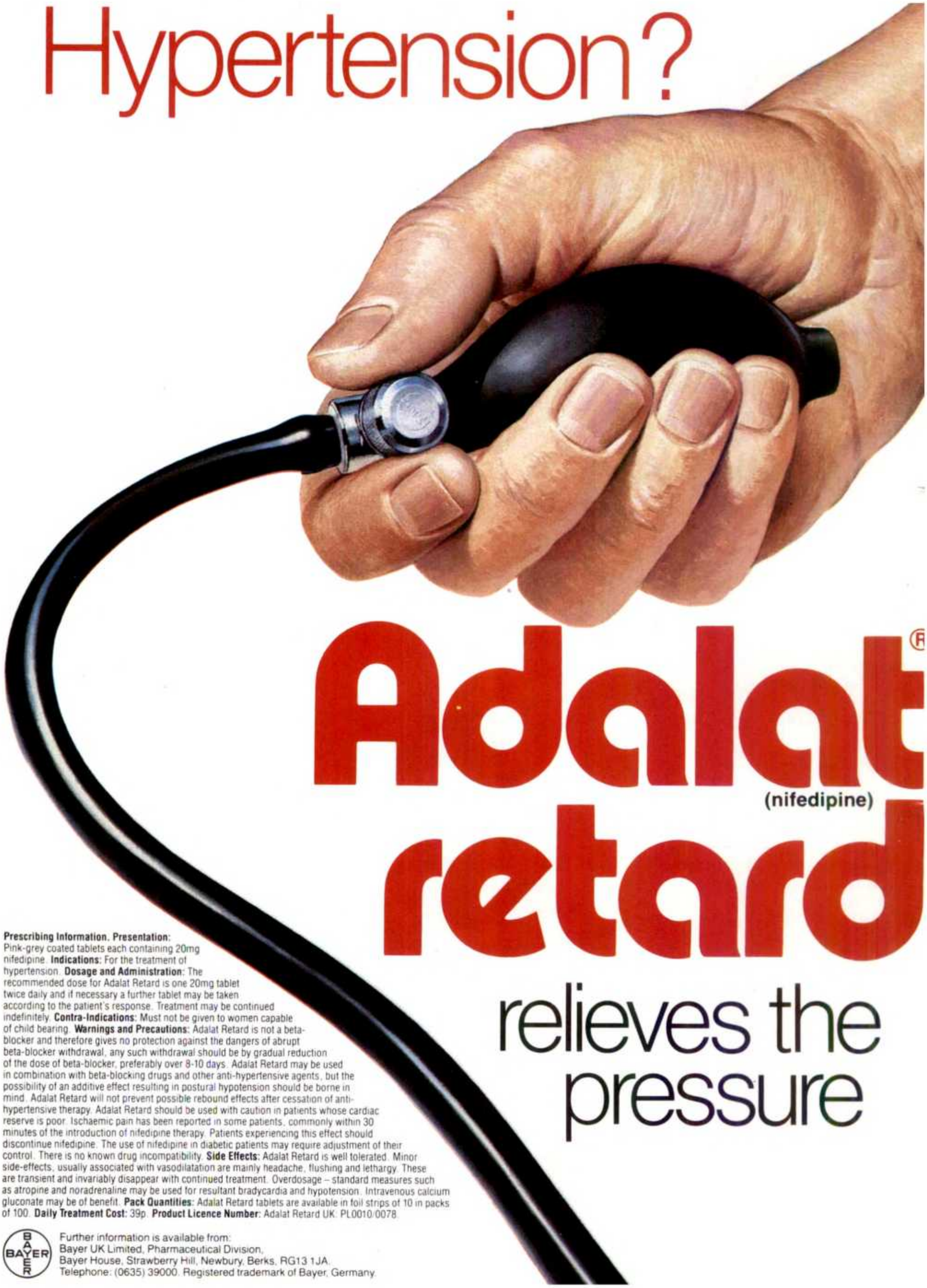

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Br Heart J 1985; **53**: 353–62

Editorial

Mitral valve prolapse associated with other disorders

Casual coincidence, common link, or fundamental genetic disturbance?

ALASDAIR D MALCOLM

From Airedale General Hospital, Keighley, West Yorkshire

Clinicians seem to enjoy describing associations between diseases, abnormalities, and features in patients they have examined. Indeed the recognition of such links is an understandable consequence of good observational powers allied to thoughtful consideration of accumulated experience and data. As mitral valve prolapse[1-4] is now recognised as a fairly common clinical entity[3-8] it comes as no surprise to find that a substantial number of published reports has accumulated linking it with a variety of other clinical conditions. With echocardiographically demonstrable mitral valve prolapse recently documented in one large study in the Eastern part of the United States in 5% of a total of 4967 people with technically adequate echocardiograms,[9] we can expect that chance occurrence of mitral valve prolapse with other disorders will not be too infrequent.[3] It is the purpose of this editorial to consider the reported associations and, with an awareness of the possibility of casual coincidence, categorise the associations according to pathophysiological mechanisms wherever possible.

Screening

Although there are certain auscultatory features characteristic of mitral valve prolapse,[2-4 10] there is a subjective element and considerable interindividual variation in what is heard through the stethoscope, and surveys of the prevalence of mitral valve prolapse could not depend on auscultatory criteria. In addition, silent mitral valve prolapse is not rare,[3 10-12] and non-ejection systolic clicks can be heard without echocardiographically demonstrable mitral valve prolapse.[3 10] The direct but non-invasive visualisation of excessive systolic bulging of the mitral leaflets by echocardiography has been the key to the widespread diagnosis of the condition[3 13 14] and it is on echocardiographic data that surveys of the prevalence of mitral valve prolapse are largely based.[3 5-10] Nevertheless, the distinction between mitral valve prolapse and certain movements of the mitral valve that may be normal is imprecise,[13] and some investigators may even have been overdiagnosing prolapse.[15] Moreover, in some subjects it may be a variant of normal[16] and present only at certain times of life.[9]

M mode echocardiography will not detect mitral valve prolapse in a significant percentage of subjects shown by angiography to have mitral valve prolapse or with auscultatory signs of the conditions[3 10 11 17 18] because of the limited view it affords of mitral valve motion.[13 14 17 18] False positive patterns of mitral valve prolapse can also be found,[3 13 17 18] but this is much less of a problem than the false negatives. Cross sectional echocardiography undoubtedly provides better spatial orientation and ease of determining the mitral annular plane than the M mode method and should now be considered the standard for diagnosis.[13 14 17-19] It is more sensitive than M mode and highly specific,[17-19] and the sensitivity can be enhanced by using selected combinations of echocardiographic signs.[19] Doppler echocardiography can detect associated mitral regurgitation but a mid to late systolic flow signal posterior to the mitral valve may be indicative of blood movement within the prolapsed leaflet[18]; more work is needed to discover the true value of duplex imaging with range gated Doppler flow detection in the assessment of and screening for mitral valve prolapse.

All surveys of the prevalence of mitral valve prolapse that have relied primarily on M mode echocardiographic criteria must be considered as likely to have underestimated the prevalence and we should now require data derived from cross sectional echocardiography, analysing multiple features.[14 19]

Classical pathology

In primary or idiopathic mitral valve prolapse[3] the

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voluminous leaflets are structurally abnormal with myxomatous degeneration and disruption of the pars fibrosa, and there is dilatation of the mitral annulus.[3 20–27] There is evidence of an abnormality of collagen.[23 26 28] The dissolution or dysgenesis of collagen in the continuous complex of pars fibrosa and chordae appears to be the basic mechanism responsible for the ballooning of the mitral leaflets.[4] It remains uncertain, however, as to whether the fundamental problem is a dyscollagenosis[26] or whether the collagen abnormalities and superimposed glycosaminoglycan infiltration giving the tissue its myxomatous appearance can develop in a valve that originally was structurally and histologically normal but for some reason prolapsed and thereby altered the magnitude and distribution of mechanical forces acting on the leaflet, annulus, and chordae.[23 26 28 29] The chordal deficiencies described by Becker and de Wit as being very common in mitral valve prolapse and relatively uncommon with normal non-prolapsing mitral valves[30] may also render the leaflets more vulnerable to mechanical damage.

This general pattern of abnormality in prolapsing mitral valves that become available for pathological examination, either by surgical excision because of severe mitral regurgitation requiring valve replacement or by death and subsequent necropsy, cannot be assumed to be the norm in all cases of mitral valve prolapse. The Framingham study data have provided powerful evidence that echocardiographic mitral valve prolapse can be a transient phenomenon at a certain stage in life, at least for women.[9] The prevalence of mitral valve prolapse (by M mode echocardiography screening, with cross sectional echocardiography for confirmation in more than 90% of subjects) declined progressively for successive decades from 16·9% for women in their twenties through 12·2% in their forties and 4·4% in their sixties to 1·4% for women of 80 years and older. In contrast, the prevalence among men showed no particular age related trend and averaged about 3%. It seems unlikely that structural abnormalities would be present in the mitral valves of a significant proportion of younger women and similarly unlikely that these would be remedied in most as they get older. Rather, we should look to factors beyond the mitral valve itself, and age related changes in left ventricular size, shape, or wall movement may be part of the explanation.

In evaluating possible associations between mitral valve prolapse and various disorders we must bear in mind that an echocardiographically prolapsing mitral valve is not necessarily abnormal in any way[13 14 16] and draw realistically limited conclusions in those conditions in which cardiac tissue has not been available for systematic pathological and biochemical study in surgical or necropsy series.

Association with abnormalities of left ventricular size, shape, or function

Excessive bulging of one or both mitral leaflets into the left atrium may be due to factors other than floppy leaflets, elongated chordae, or a dilated annulus.[3 13 31 32] Thus disturbance of the normal balance between ventricular and valvar size may cause anatomical prolapse in the absence of any pathological feature of mitral leaflets or chordae. This would occur when left ventricular size is sufficiently reduced or shape sufficiently altered that maintenance of normal leaflet position and contour during systole is impossible and some degree of prolapse into the left atrium results, as in hypertrophic obstructive cardiomyopathy.[3 32] In secundum atrial septal defect, where up to half the patients seem to have mitral valve prolapse,[3 13 33 34] the reduced left ventricular size with distorted ventricular geometry is probably often responsible for the mitral valve prolapse.[13 34] There are, however, instances where the mitral valve has become severely regurgitant and been found to have the myxomatous degeneration characteristic of primary mitral valve prolapse.[3 35] Distortion of the atrioventricular area and reduced left ventricular size have been proposed as the mechanism of prolapse in patients with progressive muscular dystrophy and straight or lordotic thoracic spines.[36] Ischaemically induced disturbance of contractile function in papillary muscles or subjacent myocardium may result in failure to maintain chordal systolic tension and so prolapse ensues[3 32 37]; this would be the most common cause of secondary mitral valve prolapse. Disturbance of left ventricular contraction with previous rheumatic carditis or viral myocarditis or with congestive cardiomyopathy may result in prolapse.[37] It has also been proposed that the abnormal sequence of ventricular activation in the Wolff-Parkinson-White syndrome can give rise to mitral valve prolapse.[37 38] but the idea that the bypass tract and prolapse are associated structural malformations within the atrioventricular region is an alternative explanation.[3]

Secondary mitral valve prolapse is probably of no special significance in most subjects, but it has been suggested that an abnormally stressed mitral valve might ultimately develop the same pathological changes found in primary mitral valve prolapse.[13] Nevertheless, when secundum atrial septal defect is accompanied by a regurgitant prolapsing mitral valve the differential diagnosis with primum atrial septal defect complicated by atrioventricular valve abnormality has to be considered and there may be surgical implications.[3] Infective endocarditis, which hardly ever occurs in isolated secundum atrial septal defect, can occur when associated mitral valve prolapse is present, and Jeresaty recommends antibiotic prophylaxis for secundum atrial septal defect with mitral valve prolapse and late systolic or pansystolic murmurs.[3] Perhaps it would be prudent to follow the same guidelines for secondary mitral valve prolapse in ischaemic heart disease.[37]

Association with congenital heart disease

Secundum atrial septal defect is the commonest reported association, as discussed in the previous section, but there are a variety of other congenital cardiac abnormalities in which an association with mitral valve prolapse has been claimed.[3 37] A retrospective study of M mode echocardiograms from 120 adults with congenital heart disease revealed mitral valve prolapse in nine of 32 (28%) patients with secundum atrial septal defect, in none of five with primum atrial septal defect, in 10 of 25 (40%) with ventricular septal defect, in five of seven (71%) with persistent ductus arteriosus, in three of five (60%) with tetralogy of Fallot, in five of 15 (33%) with pulmonary stenosis, in two of 14 (15%) with left ventricular outflow obstruction, in two of three (67%) with Ebstein's anomaly, and in four of 14 (29%) with miscellaneous other defects.[33] Among 45 children with M mode echocardiographically demonstrated mitral valve prolapse there were three cases of ventricular septal defect, one of persistent ductus arteriosus, and two of hypertrophic obstructive cardiomyopathy.[39]

Pathological studies have provided some interesting data in respect of ventricular septal defect and Ebstein's anomaly. Among 112 hearts with isolated ventricular septal defect collected over a 30 year period and restudied specifically for gross and microscopic (significant thickening of the spongiosal layer and invasion and disruption of the fibrosa by the spongiosa) evidence of mitral valve prolapse there was an overall incidence of the condition of 18%.[40] There was no significant difference in the incidence of mitral valve prolapse for the three age groups (<1 year, 1–16 years, and 17–91 years) considered. Spongiosal invasion of the fibrosa was fully developed by 3 months of age, and there was no evidence that the incidence or severity of spongiosal invasion increased between the ages of 3 months and 88 years. In no patient was the mitral valve prolapse considered to be the cause of death. Complications of the prolapse in terms of ruptured chordae, endocarditis, mitral regurgitation, and fibrin deposits at the mitral valve-left atrial angle occurred at approximately the same frequency as that reported in necropsy studies of isolated mitral valve prolapse. In the specimens with prolapse 63% also had similar involvement of the tricuspid valve, 16% of the pulmonary valve, and 5% of the aortic valve. In a separate study the hearts obtained at necropsy from 10 patients with Ebstein's anomaly of the tricuspid valve were examined for mitral valve prolapse and the condition was found in none of five hearts from patients aged 1 day to 10 months but in 3 of 5 hearts from patients aged 18 to 72 years.[41] The most severe degree of prolapse occurred in the 18 year old, whose mitral valve histology showed myxomatous change with a pronounced increase in acid mucopolysaccharide material in the leaflets.[42] These pathological studies would potentially have underestimated the frequency of mitral valve prolapse with congenital cardiac abnormalities for they depended on necropsy specimens, and mitral valve prolapse secondary to disturbances of left ventricular dynamics,[31] as in secundum atrial septal defect,[34] would have been missed.

Association with other cardiac structural abnormalities

Tricuspid valve prolapse coexists fairly frequently with mitral valve prolapse, as shown at necropsy,[3 22] on cineangiography,[3 43 44] and by M mode[3 45 46] and cross sectional echocardiography.[17 47 48] For example, in 61 symptomatic patients with auscultatory signs of mitral valve prolapse and no significant occlusive disease on selective coronary arteriography left ventricular angiography detected prolapse in 52 (84%), and right ventricular angiography showed tricuspid valve prolapse in 32 (52%); in nine cases prolapse involved the tricuspid valve alone. Although 21% of a group of 53 patients with mitral valve prolapse had concomitant tricuspid valve prolapse on M mode echocardiography, imaging of the tricuspid valve by this technique is inconsistent and cross sectional echocardiography is more often successful and provides better visualisation of the tricuspid leaflets.[17 48] Thus cross sectional echocardiography showed concomitant tricuspid prolapse in 48% of 64 patients with mitral valve prolapse[17] and in 19% of 31 patients with mitral valve prolapse.[48] Contrast echocardiography is helpful in evaluating tricuspid regurgitation in this situation.[17 47] The general observation has been made that among subjects with tricuspid valve prolapse a more severe form of mitral valve prolapse is prevalent.[17] Although it has been claimed that tricuspid valve prolapse occurs rarely as an isolated lesion,[3] careful cross sectional echocardiographic technique has been shown to be capable of demonstrating it in 6% of an assorted group of 112 subjects without mitral valve prolapse,[48] and it can be shown angiographically when prolapse is not evident on the contralateral ventricular cineangiogram.[44] Data are lacking on the histological state of prolapsing tricuspid valves where there has not been concomitant mitral valve prolapse but the prolapse may be secondary to disturbed right ventricular dynamics. A genetically determined abnormality of atrioventricular valve development or maintenance or both would explain dual valvar involvement.

Aortic valve prolapse was evaluated by cross sectional echocardiography in 50 subjects with mitral valve prolapse and no stigmata of Marfan's syndrome.[47] Twelve (24%) subjects had redundant aortic leaflets bulging into the left ventricular outflow tract during diastole, and most of these subjects also had aortic regurgitation. In one subject who underwent mitral and aortic valve replacement for severe heart failure both excised valves showed characteristic myxomatous degeneration. In an earlier study of 112 subjects with mitral valve prolapse successful cross sectional detailed imaging of the aortic valve was achieved in 77 and a prolapse pattern identified in 17 (22%), 16 of whom showed increased echo reflection from aortic leaflet tissue and four of whom had aortic regurgitation.[17] The aortic root measurement on M mode echocardiography was normal in the 60 subjects with mitral valve prolapse without aortic valve prolapse but enlarged in six of the 17 subjects with both aortic valve and mitral valve prolapse. Other evidence of myxomatous involvement of the aortic valve in some cases of mitral valve prolapse has been reported with aortic leaflets thickened or folded on cross sectional echocardiograms, systolic oscillation and multiple leaflet echoes on M mode scans, and confirmation of the myxomatous nature of one aortic valve replaced at operation.[49] The myxomatous degeneration[25] which typifies primary mitral valve prolapse is therefore not confined to atrioventricular valve tissue in certain individuals, and comprehensive clinical evaluation of the subject with mitral valve prolapse should be conducted with this in mind. Cross sectional echocardiography is the major tool for precise evaluation of this sort[17 47] and may even show triple valve involvement.[47]

Atrial septal aneurysm combined with mitral valve prolapse has been found at necropsy in two patients,[50] but no mention was made of myxomatous degeneration in the leaflet tissue. Bulging of the aneurysm can be seen on cross sectional echocardiography, and there is a report of five patients with the combined conditions, four of whom also had tricuspid valve prolapse.[51] A developmental abnormality affecting the tissue of interatrial septum and mitral valve can be supposed.[50 51]

There are a number of reports of a definite association between pre-excitation atrioventricular pathways and mitral valve prolapse.[3 37 38 52–55] The relation with the Wolff-Parkinson-White syndrome was first reported by Gallagher *et al* in 1975 with seven cases of mitral valve prolapse among 68 patients with the Wolff-Parkinson-White syndrome and attacks of arrhythmia that were sufficiently frequent or of such severity as to be disabling or life endangering.[52] The Lown-Ganong-Levine syndrome has been found in association with mitral valve prolapse in several instances.[3 53–55] Of 12 patients with paroxysmal supraventricular tachycardia, three had the Lown-Ganong-Levine syndrome, one the Wolff-Parkinson-White syndrome type A, and eight normal electrocardiograms.[54] Six of the eight patients with normal electrocardiograms were, however, shown on electrophysiological study to have atrioventricular bypass tracts. This evidence suggests that supraventricular tachycardia in patients with mitral valve prolapse could often be related to bypass tracts that, if the surface electrocardiogram is normal, will require special electrophysiological studies to enable diagnosis, and the authors felt that there may be a developmental link between the consistently left sided bypass tracts and the mitral valve prolapse.[54] These data from patients with major arrhythmia problems[52 54] have to be kept in perspective when dealing with subjects with mitral valve prolapse and little or no symptomatology of this sort. In two British series, without particular selection for problems with tachyarrhythmias, there were no cases of short PR interval of any sort among the study groups of 85[11] and 182[12] subjects with mitral valve prolapse.

Problems of cardiac impulse formation and conduction are also encountered in subjects with mitral valve prolapse.[3 31 56 57] Sixty symptomatic patients with mitral valve prolapse underwent electrophysiological study; 49 had documented arrhythmias and 28 had experienced syncope.[57] Spontaneous second or third degree atrioventricular block was documented in eight patients, and 10 had chronic bundle branch block. Electrophysiological study showed abnormal sinus node function in eight patients, prolonged HV interval in 10, intra-Hisian delay in nine, and functional bundle branch block in 15. Dual atrioventricular nodal pathways were detected in 24 patients. Comparison with 101 similarly symptomatic patients without mitral valve prolapse showed a greater prevalence of dual atrioventricular nodal pathways and functional bundle branch block in the patients with mitral valve prolapse, but the other features were not significantly more or less common in the control group and therefore probably represent casual coincidence with mitral valve prolapse.

Association with thoracic spine and chest wall abnormalities

Narrow anteroposterior chest diameter, straight back, and pectus excavatum deformity are commonly associated with mitral valve prolapse.[3 31 58–62] The mitral valve undergoes differentiation to its final form between the thirty fifth and forty second day of fetal development, when the vertebral column and thoracic cage are beginning their chondrification and ossification. Any influence on fetal development at this stage may therefore affect both the mitral valve and bony thorax.[58] In one radiological study in Hong Kong the metacarpal index was also measured, and, somewhat surprisingly, among the study group of 115 subjects with mitral valve prolapse almost all with abnormal metacarpal indices had normal chest measurements (ratio of anteroposterior to transverse diameter)[62]; the reason for this dissociation is obscure, but it does suggest that in respect of aetiology subjects with mitral valve prolapse are likely to be heterogeneous and that a substantial proportion are unlikely to have anything to do with Marfan's syndrome.

Breast development may be impaired in some women with mitral valve prolapse, and the explanation could be similar to that for abnormalities of the bony thorax associated with mitral valve prolapse—namely, that both breast and mitral valve are of mesenchymal origin and undergo simultaneous primordial development.[63] In a group of 27 patients with hypomastia referred for elective augmentation mammoplasty, 13 (48%) had mitral valve prolapse on both M mode and cross sectional echocardiograms compared with only two (6%) of 33 controls.[63] Conversely, of 28 women selected consecutively from the echocardiographic data base at the same medical centre during the same 14 month period with mitral valve prolapse shown on echocardiography, 17 (61%) had hypomastia; hypomastia was found in eight (24%) of the controls. Whether the explanation for the link between hypomastia and mitral valve prolapse is entirely explicable in terms of embryological and mesenchymal dysplasia is a matter of dispute.[64] With a much higher prevalence of mitral valve prolapse among lean persons than among those of above average body weight in the Framingham study[9] and with other data indicating a correlation with slim build and below average weight,[4 61 64] the hypomastia may simply be due to reduced contribution of adipose tissue to breast size.[64]

Clinicians should be aware of the increased chance that mitral valve prolapse is present when thoracic skeletal deformities or hypomastia (defined as a breast size ≤200 ml[63]) are present. Familial clustering of cases of mitral valve prolapse does occur,[3 65–67] but, although there is some evidence of an autosomal dominant mode of inheritance,[3 61 66 67] it appears that convincing proof of this hypothesis is lacking at present.[9 68] Nevertheless, diagnostic appraisal of possible mitral valve prolapse in the potentially affected close relatives of subjects with primary mitral valve prolapse seems warranted.[68]

Association with inherited disorders characterised by weakness or laxity of certain tissues

It is well established that mitral valve prolapse is an integral part of many inherited connective tissue disorders,[3 4 31 68] best known among which are the Marfan and Ehlers-Danlos syndromes.

In an M mode echocardiographic study of 35 patients with the Marfan syndrome mitral valve prolapse was found in 91%.[69] In 50 consecutive patients with the syndrome reported by Pyeritz and McKusick, 24 (48%) had midsystolic clicks with or without late systolic murmurs and 29 (58%) had echocardiographic (probably M mode for most cases, although not specified) evidence of mitral valve prolapse.[70] Among 13 patients with typical Marfan's syndrome, fusiform aneurysms of the ascending aorta, and chronic aortic regurgitation studied at necropsy[71] mitral valve prolapse was evident in only four, but the mitral annulus was larger than normal in most of the hearts and histological examination of the mitral leaflets showed excessive acid mucopolysaccharide material in all cases. Despite the frequency with which mitral valve prolapse is encountered in those with the Marfan syndrome, and despite some tendency for mitral valve prolapse to be associated with a marfanoid habitus,[61 68] the suggestion[72] that mitral valve prolapse represents a forme fruste of Marfan's syndrome has now been firmly rejected.[3 68]

The Ehlers-Danlos syndrome is a group of inherited defects of connective tissue sharing certain physical features such as hypermobile joints, fragile skin, bruising, hernias, and various deformities including pectus excavatum[73]; there are several reports of its coexistence with mitral valve prolapse.[3 74–77] In type IV Ehlers-Danlos syndrome a propensity for aortic rupture[73] is a striking point of similarity with the Marfan syndrome. In a family with type IV Ehlers-Danlos syndrome cross sectional echocardiography detected mitral valve prolapse in eight of 10 subjects examined, and when production of type III collagen[73] was assessed by use of cultured fibroblasts from skin biopsy specimens it was found to be deficient in all eight echopositive cases and normal in the two cases with normal echocardiograms.[77] Abnormal type III collagen is the fundamental biochemical defect in Ehlers-Danlos syndrome type IV[73] and analysis of a surgically excised valve from a patient with mitral valve prolapse and severe mitral regurgitation, who did not have the Marfan or Ehlers-Danlos syndrome, has shown a pronounced deficiency of type III collagen.[78] More recent data from Australia, however, have shown that in 19 myxomatous mitral valves obtained at valve replacement surgery there is increased production of several types of collagen, in particular type III,[28] and prompts speculation that the glycosaminoglycan infiltration and cellular proliferation in the valves are part of a repair process. The microstructural basis for mitral valve prolapse may thus be different in primary mitral valve prolapse compared with the mitral valve prolapse encountered in the inherited disorders of collagen synthesis.

Hypermobility of joints has been found to be more common in 21 subjects with echocardiographically identified primary mitral valve prolapse than in matched controls, but there was no significant difference in skin thickness, skin elasticity, or prevalence of either skeletal deformity or marfanoid habitus between the groups.[79] Other investigators[12] have not found this undue joint mobility, but among 182 patients with M mode echocardiograms showing mitral valve prolapse 22 (12%) were noted to have had a herniorrhaphy in the past, perhaps indicative of a tendency for weakness of collagen common to mitral valve and extracardiac tissue.[12] Patients with hypermobile joints attending a rheumatology clinic were found to have auscultatory and M mode echocardiographic evidence of mitral valve prolapse more frequently than control patients with normal joint mobility scores.[80] Laxity of joints may be associated with a more widespread abnormality of collagen within the cardiovascular system. This is suggested by the finding of an increased aortic compliance (as measured by a continuous wave Doppler ultrasound technique) in 44 of 72 patients with the hypermobility syndrome,[81] some of whom were also shown to have collagen abnormalities on biochemical analysis and electron microscopy of skin biopsy specimens.

The data cited in respect of the Marfan and Ehlers-Danlos syndromes give reasonable grounds for expecting to find mitral valve prolapse in a high proportion of patients with other generalised disorders of connective tissue,[3] where structural weakness of mitral leaflets, chordae, and annular tissue would be the cause of the prolapse. This expectation is fulfilled in a study of pseudoxanthoma elasticum,[82] but in osteogenesis imperfecta, despite reports of two regurgitant prolapsing mitral valves requiring replacement[83] and of one mitral valve showing severe myxomatous degeneration,[84] an M mode echocardiographic study of 20 patients detected mitral valve prolapse in only one.[85] An increased prevalence of mitral valve prolapse has been shown with cross sectional echocardiography in 15 patients with von Willebrand syndromes, among whom mitral valve prolapse was found in 60% compared with 13% of matched controls[86]; the concept of a linked mesenchymal dysplasia was proposed as a unifying hypothesis to explain the association of mitral valve prolapse with this vascular endothelial abnormality and with various skeletal and connective tissue dysplasias already mentioned.[86]

Association with disorders of skeletal muscle

Although there are several reports of an increased prevalence of mitral valve prolapse in myotonia atrophica,[3 87] there is no clear evidence either of myxomatous degeneration of mitral valve tissue or of myocardial involvement with dysfunction localised so as to impair mitral valve function.[87] A recent prospective study of 25 adults with myotonia atrophica showed that on cross sectional echocardiography mild mitral valve prolapse was present in three and moderate mitral valve prolapse in four cases.[88] The significance of mitral valve prolapse in myotonia atrophica and in other muscle diseases requires further elucidation with larger series and provision of some correlative cardiac pathological data.

Association with endocrine disorders

When Jeresaty's monograph of mitral valve prolapse was published in 1979[3] it contained but one reference to an associated endocrine disorder and that was to a report[89] of a single case of acromegaly with a systolic click and murmur complicated by streptococcal endocarditis. How surprising then that it should have taken until 1981 for an association with one of the more common disturbances of endocrine function—namely, hyperthyroidism—to be reported.[90] Impressed by what seemed to be a high frequency of mitral valve prolapse in patients with hyperthyroidism and aware of the evidence that adrenergic tone is increased both in hyperthyroidism[91] and in symptomatic mitral valve prolapse,[4 92] clinicians at the Temple University School of Medicine in Philadelphia looked for mitral valve prolapse in 40 patients with hyperthyroidism.[90] The diagnosis of mitral valve prolapse depended on auscultatory and echocardiographic (both M mode and cross sectional) assessment, and in only one instance (a hyperthyroid patient) was the diagnosis made on auscultatory findings alone. Sixteen of 39 (41%) patients with Graves' disease and one patient with toxic nodular goitre had mitral valve prolapse compared with seven of 40 (18%) patients in a control group. The prevalence of mitral valve prolapse did not differ significantly between those who were hyperthyroid at the time of evaluation and those who were not and seemed unrelated to the sex or race of the patient.

The link between mitral valve prolapse and hyperthyroidism is further explored in a much larger study from Israel reported in this issue of the journal (p 374–7).[93] The investigators used both M mode and cross sectional echocardiography to detect mitral valve prolapse. Among a group of 126 hyperthyroid patients there were 12 (9·5%) cases of mitral valve prolapse, which is not significantly different from the prevalence of 5·4% in the control group of 111 subjects. When the 49 patients with Graves' disease were considered separately, however, the prevalence was 16·5%, and this difference is significant. As in the American study[90] it made no difference whether the patients were hyperthyroid or had become euthyroid. The prevalence of hyperthyroidism among 64 subjects with mitral valve prolapse was also assessed; in one case the laboratory tests indicated hyperthyroidism, but clinical features of hyperthyroidism were lacking.

The basis for the association between mitral valve prolapse and Graves' disease is a matter of conjecture.[90,93] It would seem that the valvar prolapse is not attributable to myocardial dysfunction caused by a direct effect of high concentrations of thyroid hormones, and there are no data on the gross morphology or histology of mitral valves from patients with this combination. Proof of a common autoimmune mechanism[90,93,94] would probably require immunohistological studies of mitral valve and thyroid tissue. Certain histocompatibility antigens have been reported to be associated with mitral valve prolapse[90,93,95] and with Graves' disease,[90,93] but the pathophysiological mechanisms by which this might cause the two disorders remain undetermined. Perhaps the best guess that can be made at present is to suppose a defect of genetic coding for control of mitral valve tissue formation, turnover, or subsequent modification at a locus adjacent to one exerting some influence over the control of thyroid function or all three. This could be the basis for some of the other clinical associations[63,68,86] and is worthy of further investigation.

Conclusion

There is still much to be learned about mitral valve prolapse,[4,96,97] and in clinical practice major issues which remain imperfectly resolved include the pathogenesis and management of accompanying chest pain,[4,98] identification and protection of those subjects at risk of thromboembolic complications[4,97] or arrhythmic sudden death,[99,100] and prophylaxis against endocarditis.[97,101] There is no doubt that anatomical prolapse of mitral leaflets is common, but in only a small proportion of subjects should we consider this to be "abnormal."[16] In some it will be evanescent. It may be some years before pathological studies on mitral valves from an appreciable number of supposed "normal variant" subjects with mitral valve prolapse can be reported. Improved cross sectional echocardiographic instrumentation and meticulous attention to details of technique will enable mitral leaflet thickness to be determined, as very recently reported by Chandraratna *et al*,[102] and this may be the key to distinguishing between "normal" prolapsing mitral valves and pathological[96] forms of mitral valve prolapse. A completely new set of cross sectional echocardiographic surveys of mitral valve prolapse in unselected populations and in subgroups of patients with the various conditions suspected to be associated with mitral valve prolapse will now have to be carried out, and it is to be hoped that the opportunity will be taken, wherever possible, to ascertain the morphology, histology, and histochemistry of the mitral valve and any other features of cardiac pathology.

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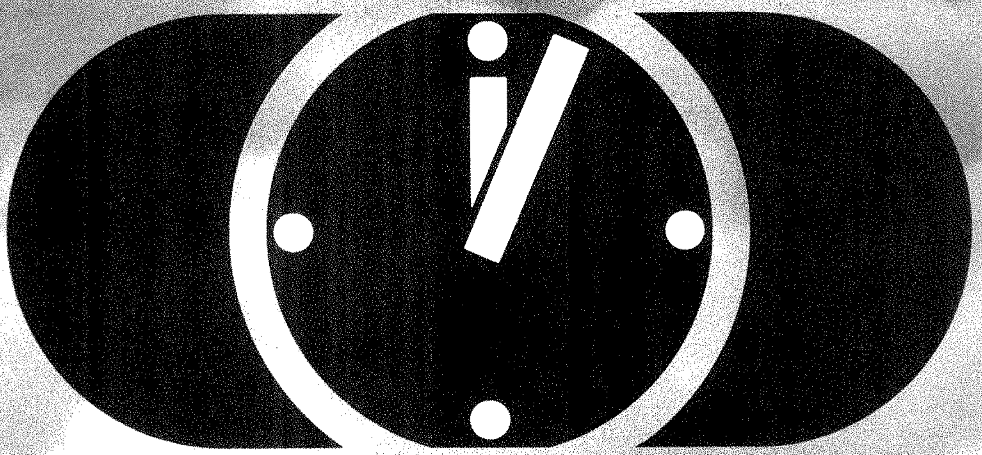

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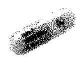
Angina, anxiety, essential tremor, thyrotoxicosis, prophylaxis of migraine.			
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Br Heart J 1985; 53: 363–73

Review

Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina

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The clinical management of acute myocardial infarction and crescendo angina as well as the prevention of sudden ischaemic death require accurate knowledge of the underlying arterial pathology. It is on just this aspect that until recently there has been disagreement particularly among pathologists. In brief, this controversy was concerned with whether coronary artery thrombi were or were not directly responsible for all three clinical pictures of acute ischaemia.

Resolution of the controversy has been derived from coronary angiography in life in patients with acute infarction and crescendo angina and from detailed pathological studies. These latter studies differ from many carried out previously by the use of postmortem coronary angiography and histological reconstruction of the microanatomy of occlusive lesions.

Findings in life

Clinical angiography has shown that the incidence of occlusion in the coronary artery supplying a myocardial infarct is very high during the early period after the onset of symptoms. Figures of around 90% are consistently reported within an hour of the appearance of electrocardiographic changes of infarction, but the incidence of acute occlusions thereafter falls to around 50% at 12–24 hours.[1 2] The implication is that blood flow has been restored by natural processes which, judged by their rapidity, can only be by lysis of thrombus or relaxation of spasm or a combination of the two. A number of clinical angiographic appearances—including persistent retention of contrast medium by intraluminal material, an irregular or lobulated margin to the occlusion, and filling defects within the lumen—have been taken to indicate a thrombotic occlusion.[3] In postmortem coronary arteriograms areas of stenosis with ragged margins and intraluminal transluscency have been shown to be a reliable indicator of the presence of thrombus.[4] The success of either intracoronary streptokinase infusion or systemic streptokinase-plasminogen activator in restoring arterial patency strongly suggests that thrombus is a major element in the occlusion. Flow can be restored in 72–96% of such cases[3 5–8] using intracoronary infusion and in 45–65% of cases using intravenous infusion of fibrinolysins.[9] Fibrinolytic agents that specifically bind to recent thrombus[10] may well improve the latter rate. As the arterial flow is restored by fibrinolysis a sequence of angiographic appearances develops which includes all those taken to indicate the presence of thrombosis.[3 11–13] Such appearances, in particular intraluminal filling defects, would be most unlikely to occur if the occlusion had been due purely to spasm of an atheromatous artery.

After fibrinolysis, in most cases but not all, a high grade stenotic lesion is usually found in the artery supplying the area of infarction.[6 7 14 15] After fibrinolysis thrombosis recurs in up to 25% of cases,[6–8 11 12] particularly in those with the higher grades of residual stenosis.[16]

In crescendo angina, the causative role of thrombus is less firmly based, but angiographic appearances suggesting non-occlusive (mural) thrombus to be present have been found in 85% of cases[17–19] or even in all cases.[20] In cases where an acute infarct has developed complete arterial occlusion has been found.[11 19] The beneficial effect of aspirin treatment in reducing the risk of sudden death and acute infarction in cases of crescendo angina also points to an

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underlying thrombotic process.[21]

Thus there are compelling reasons to believe that thrombus plays a major role in both acute myocardial infarction and in crescendo angina. What has been added by these clinical studies is the evidence that thrombosis is a rapidly changing dynamic process reflecting equally rapid changes in the arterial lesion.

Necropsy findings

Recent pathological studies, in which the coronary thrombi found in fatal cases of acute myocardial infarction were reconstructed from serial histological sections, have shown that virtually all were related to rupture or fissuring of atheromatous plaques.[22 23] Rupture of a plaque leads to free communication between the lipid content of the plaque and the blood flowing within the arterial lumen. Dissection by blood from the lumen into the plaque, in many cases, results in a large intraintimal thrombus rich in platelets. Over the site of rupture thrombus develops within the lumen and often propagates distally into segments of the artery without significant intimal disease. Such studies emphasise that the head of the thrombus in relation to the plaque is different from the thrombus propagating distally[24]; the former is rich in platelets, the latter contains a higher proportion of fibrin. These postmortem studies have usually been carried out in cases where a large regional infarct is found at necropsy and the coronary artery is totally occluded, the patient having lived for at least 24 hours after the onset of symptoms.

Study of patients who die suddenly of ischaemic heart disease[25] shows that 95% of such cases have an acute evolving coronary arterial lesion. These lesions are also atheromatous plaques undergoing fissuring or rupture. All the clinical angiographic appearances regarded as indicating thrombosis are present also in postmortem angiograms in sudden ischaemic death (Figs. 1 and 2). Histological examination confirmed that in 74% of cases there was recent thrombus present in the lumen, but this did not necessarily totally occlude the vessel. In a further 21% there were plaque fissures with recent thrombi within the intima but not in the lumen. Compared with that in patients dying in hospital with established myocardial infarction the

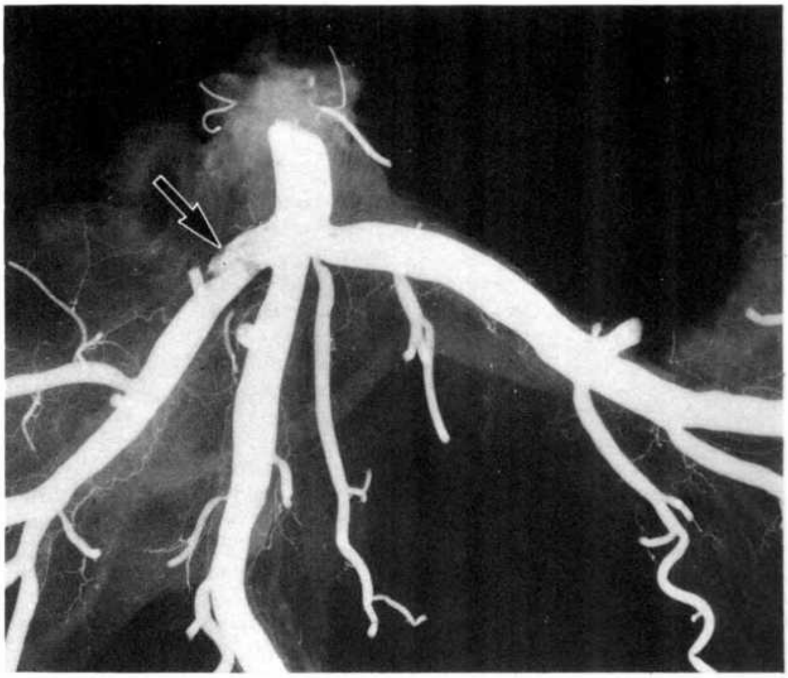

Fig. 1 *Postmortem angiogram of a man aged 44, who had no previous history of angina and was extremely fit. During a game of squash he suddenly felt unwell with chest pain and died 30 minutes later. The left anterior descending artery divided into two major branches immediately after the origin. One of these showed an intraluminal filling defect (arrow) associated with an irregular intimal outline. Histology confirmed a fissure of a plaque with overlying thrombus. The remainder of the coronary artery tree was angiographically and histologically normal.*

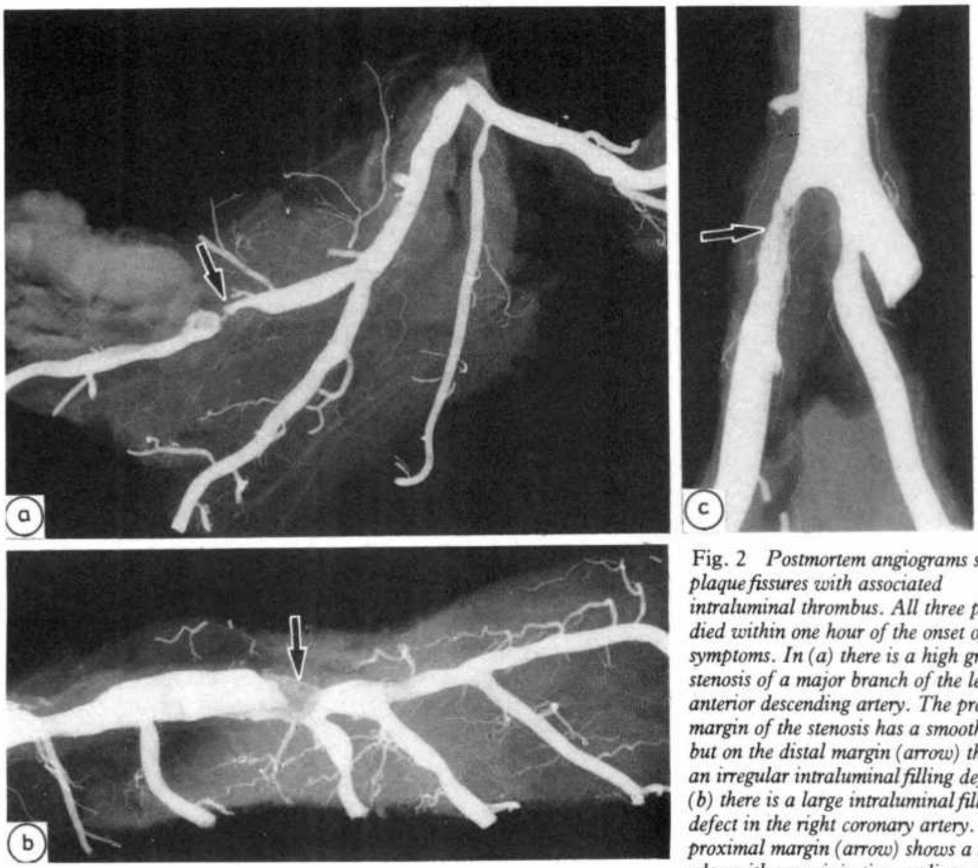

Fig. 2 *Postmortem angiograms showing plaque fissures with associated intraluminal thrombus. All three patients died within one hour of the onset of symptoms. In (a) there is a high grade stenosis of a major branch of the left anterior descending artery. The proximal margin of the stenosis has a smooth edge, but on the distal margin (arrow) there is an irregular intraluminal filling defect. In (b) there is a large intraluminal filling defect in the right coronary artery. The proximal margin (arrow) shows a straight edge with some injection medium outside the lumen. In (c) there is a translucent (arrow) line projecting into the lumen with a small linear intraluminal filling defect. In all three cases good distal filling of the vessel was present.*

incidence of a totally occlusive thrombus with distal propagation is low in sudden ischaemic death. Thus the lesions in the coronary arteries in cases of sudden ischaemic death are essentially the same as those found in cases of acute infarction but have a lesser degree of intraluminal thrombus formation.

Events in a dynamic process

Taking these clinical and pathological findings together a probable sequence of events can now be proposed. Atheromatous plaques, as seen in arteries distended and fixed at physiological pressures, bulge outward toward the media[26 27] (Fig. 3). In lipid rich plaques there is a crescentic mass of cholesterol and its esters, the lipid pool, separated from the lumen by fibrous tissue. This fibrous cap is often thinnest over the points of the crescentic shaped plaque. Rupture of the fibrous cap (Figs. 4–6) allows dissection into the intima by blood from the lumen into the lipid pool of the plaque. A mass of thrombus rich in platelets, but also containing some red cells and fibrin, forms within the intima and leads to considerable expansion of the plaque. Over the site of rupture, thrombus forms in the lumen but this mass of luminal thrombus initially does not occlude the lumen but waxes and wanes in size over hours or even days. The amount of thrombus forming within the lumen is not always directly proportional to the magnitude of the exposure of lipid in the plaque. Some patients (Fig. 7) may have a massive thrombotic response within the lumen with minimal fissuring. Ultimately, the intraluminal thrombus may grow to become totally occlusive or be completely lysed and the plaque fissure reseal, stabilising

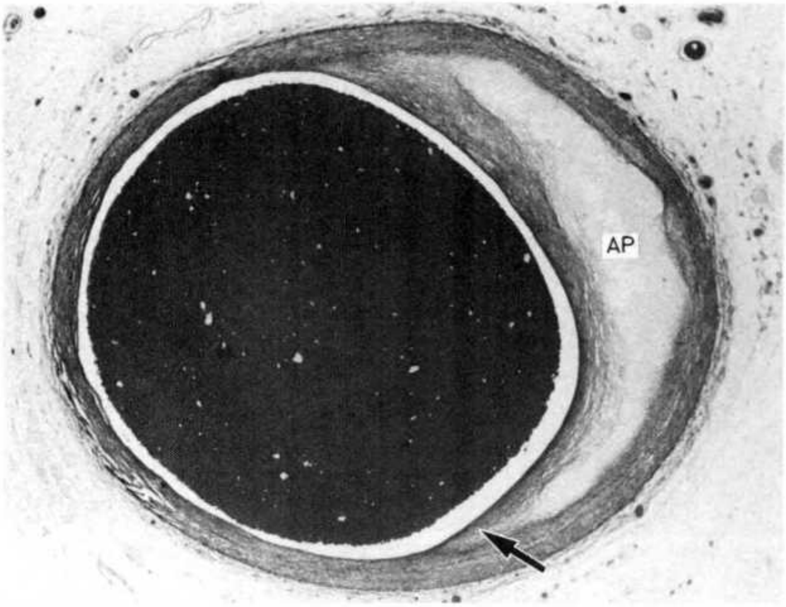

Fig. 3 *Transverse histological section of a coronary artery perfused and fixed at 100 mm Hg. No significant stensosis is present. The lumen contains angiographic medium and is round in outline. The plaque (AP) is a crescentic mass of free lipid in the intima. The lipid pool is separated from the lumen by a fibrous cap which is thinnest over one point of the crescent (arrow).*

the atheromatous plaque, albeit now considerably larger than before. By these processes patients with crescendo angina or those who suffer sudden ischaemic death have coronary artery lesions in the earlier stages of plaque fissuring. Patients who develop an established regional infarction are those in whom the thrombus had occluded the lumen at least for long enough to induce myocardial necrosis (Figs. 8 and 9). Experimental evidence suggests that this may need to be only 18 minutes of total occlusion.[28]

The basic arterial pathology of sudden ischaemic death and acute myocardial infarction is thus identical, only differing in being at different stages of the same process. The question is now posed as to why some patients should suddenly die of ventricular fibrillation before the arterial lesion is fully occlusive. Here the pathologist can give no firm answer but only hypothesise. In a small proportion of cases dissection from the lumen into the intima raises a tissue flap giving a degree of mechanical obstruction. In a larger proportion of cases the plaque has been suddenly increased in volume by thrombosis within the intima and in such circumstances the plaque encroaches on the lumen to the extent of suddenly increasing the degree of obstruction. When thrombus develops within the lumen it is a potential source of platelet emboli into small vessels in the myocardium. Some investigators have reported a high incidence of platelet emboli within the myocardium at necropsy in cases of sudden ischaemic death.[29 30] Sudden death may thus be the myocardial equivalent of transient cerebral ischaemic attacks due to platelet emboli arising from fissured and ulcerated atheromatous plaques in the carotid arteries. Finally, tearing of the intima and consequent deposition of thrombus could invoke local arterial spasm. An element of spasm in the total occlusions causing myocardial infarction has been reported[31] but is probably rare.[12] It seems certain that many patients do survive plaque fissuring without developing any clinical symptoms, and myocardial susceptibility to ventricular fibrillation must be an important and additional factor in precipatating sudden ischaemic death in certain individuals.

By this concept of the vascular pathology the three acute cardiac ischaemic presentations have a common basis (Fig. 9). Patients with a plaque fissure but who escape the three acute clinical expressions will be left with atheromatous plaques far larger than previously, and such episodic plaque growth[32] is an important factor in the developement of stable angina.

Previous contradictions explained

If the proposed mechanisms are true then much in the past that has apparently been contradictory can be

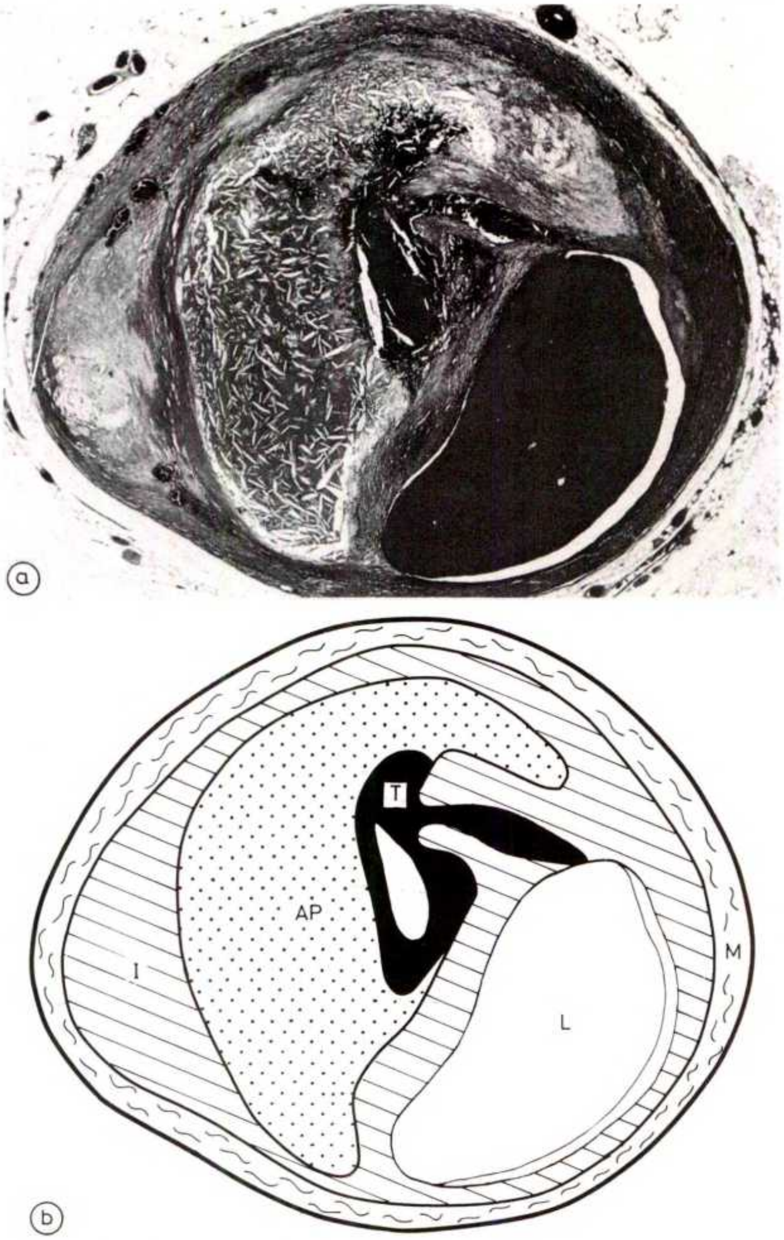

Fig. 4 *Transverse histological section of a fissured plaque (AP) (a) with accompanying diagram (b). Angiographic medium is present in the lumen (L); despite the vessel having been perfuse-fixed the plaque bulges into the lumen. A fissure extends from the lumen into the plaque, which contains a mixture of angiographic medium and thrombus (T). No intraluminal thrombus is present at this point. I, intima; M, media.*

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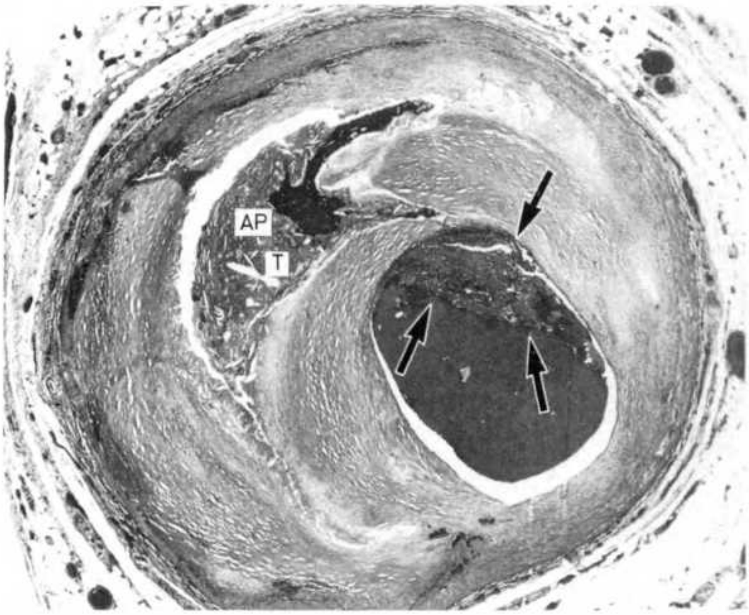

Fig. 5 *An adjacent distal histological section shows the plaque (AP) is smaller at this point but still contains injection media and thrombus (T). Mural thrombus (arrows) is present projecting into the lumen and attached at the intima close to the fissure site.*

explained. If thrombi evolve and regress over a relatively short period of time a pathologist carrying out a necropsy cannot have a precise picture of the state of the coronary arteries some days earlier when the patient first developed chest pain. Those pathological series reporting a high incidence of coronary thrombi[33-36] are biased towards patients with large regional infarcts dying in hospital. It is just such cases that have major plaque fissures with persistent total occlusion and inexorable distal propagation of thrombus. Series that report a lower incidence of thrombosis[37-40] probably contain a higher proportion of cases with smaller infarcts or even sudden death, in which the associated plaque fissure was less major and intraluminal thrombus smaller. These smaller thrombi may have spontaneously lysed before death or not been discovered at necropsy.

The acute arterial lesions associated with sudden ischaemic death are smaller than those of regional infarction and require more technical expertise for their demonstration. As there is usually no infarct recognisable at this stage the pathologist is not focused to examine a particular artery. Few of the reported studies of sudden ischaemic death have used techniques that would demonstrate the arterial pathology with certainty. Postmortem arteriography is almost certainly necessary unless the pathologist is unusually meticulous. Larger, more easily detected, thrombi are likely to be present in patients who have lived longest from the onset of symptoms, and this is the explanation of the often quoted work of Spain and Bradess,[41] who found the incidence of coronary thrombi to rise with the time interval between the onset of pain and death. A study of sudden ischaemic death in which postmortem angiography was used found thrombi in a high proportion of cases with no relation to the time interval.[25]

Once it is accepted that distal propagation of thrombosis occurs from a proximal nidus the discordant reported results of radiolabelled fibrinogen studies are easily explicable. Erhardt *et al* gave radiolabelled fibrinogen to patients with acute infarction as soon as possible after the onset of pain.[42 43] In those who died radiolabel was found at necropsy in the thrombus. These results led to the hypothesis that thrombus was secondary to and not the cause of infarction. This view was effectively quashed by Davies *et al* and Fulton and Sumner,[24 44] who by similar techniques showed the head of the thrombus over the plaque to be radionegative, the distal tail only being positive. This work is entirely in accord with the current pathological concept being propounded.

Clinical studies of patients resuscitated from apparent sudden death show that only a proportion developed acute myocardial infarction,[45 46] which has

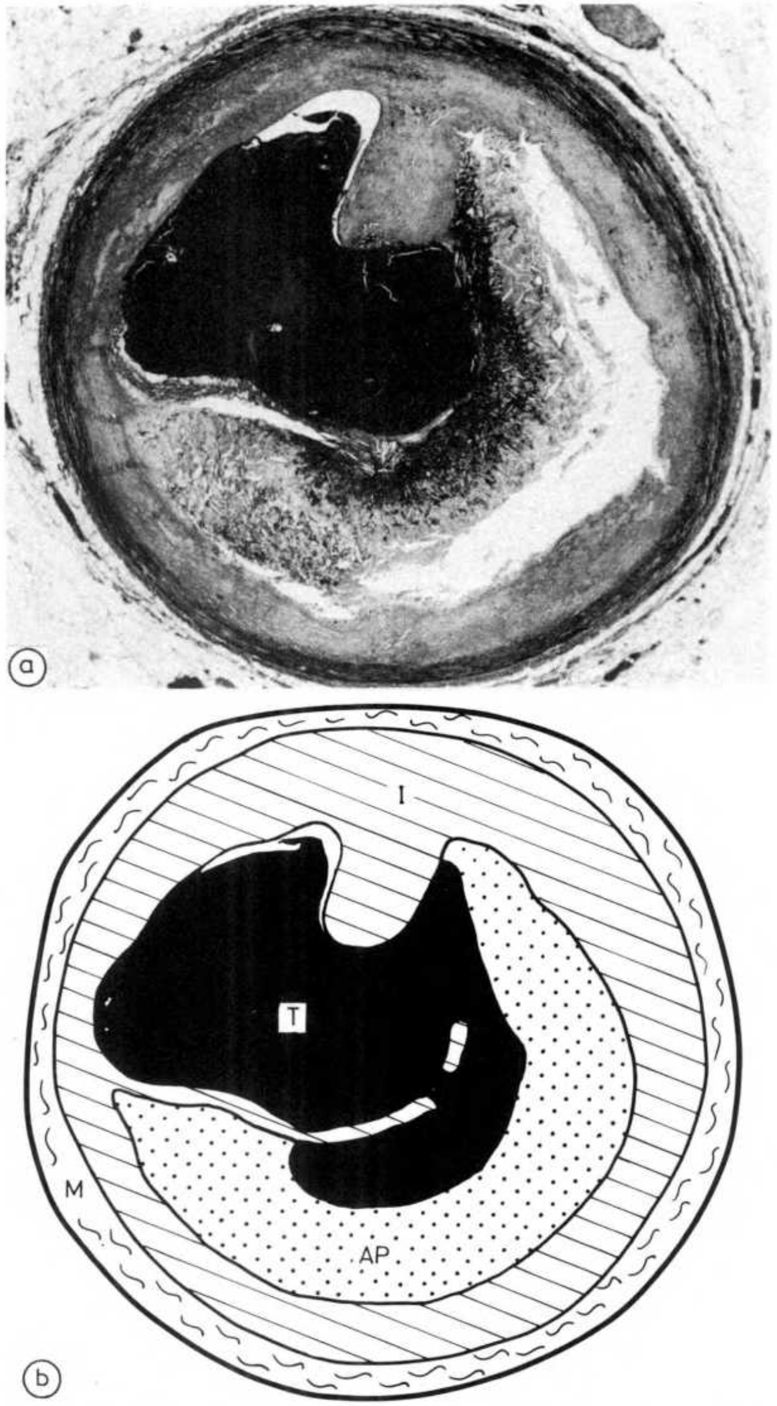

Fig. 6 *Histological cross section of a major plaque rupture (a) and accompanying diagram (b). The plaque (AP) has a large defect in the fibrous cap, through which a dumb bell mass of thrombus has formed, part being within the plaque and part virtually occluding the lumen.*

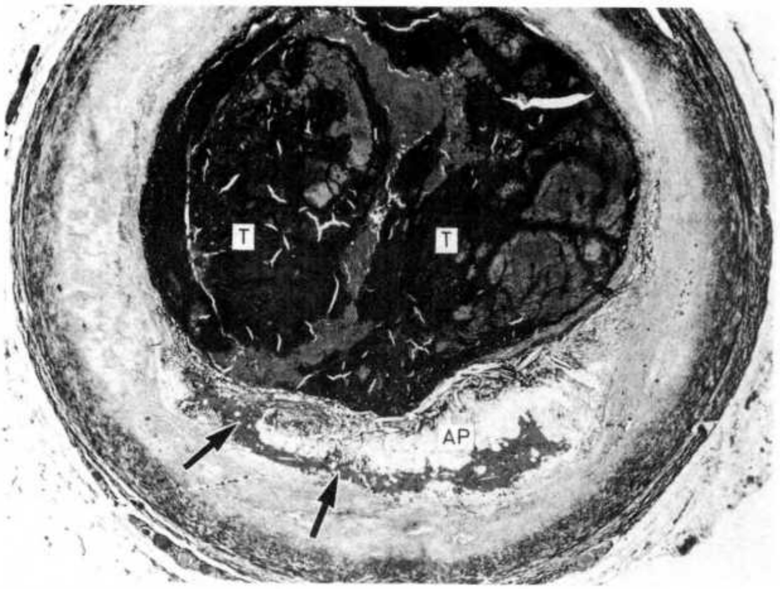

Fig. 7 *Minimal plaque fissuring associated with massive intraluminal thrombus. The plaque itself (AP) was very small, but injection media (arrow) passed easily into the lipid pool, which also contains thrombus. The lumen is occupied by a large mass of dark staining thrombus (T), which is mixed with injection media.*

been interpreted as indicating that "sudden ischaemic death" is bimodal—a group with coronary thrombosis and a group without. This view is probably an oversimplification, and it is more likely that every individual had a plaque undergoing fissuring but only a subset developed an intraluminal thrombus which was totally occlusive for long enough in time to cause infarction. In the remainder the intraluminal thrombus was not of this magnitude and subsequently lysed allowing the plaque to restabilise.

If it is accepted that plaque fissuring is a random event in lipid rich plaques there are some clinical corollaries. A proportion of patients with infarction or pending sudden death have been unfortunate enough to develop fissuring in one of the few plaques they possess. Their prognosis, if they survive, may be excellent without a further episode for many years. In contrast a patient with numerous plaques has a higher risk of repeated episodes.

Those plaques which do undergo rupture usually have a large lipid rich pool. It is often assumed that these will cause sufficient stenosis to be recognised at clinical angiography. Study of the relation of the previous degree of stenosis to thrombosis suggests that thrombosis tends to occur on plaques where the lumen has already been reduced by more than 50% by diameter.[40] It is, however, very difficult to measure accurately the previous stenosis caused by a plaque that has extensively fissured. Data on the degree of stenosis present in clinical angiograms after treatment of coronary thrombosis by fibrinolysis do not contribute since the plaques in question will have been enlarged by a sequestered acute intraintimal thrombus. It is far from clear what effect lysis has, if any, on this intraintimal component. The residual stenosis does, however, decrease over days or weeks suggesting that remodelling of the plaque must occur.[7] Pathological studies of cases of sudden death,[25] however, do suggest that fissuring can develop in plaques which are causing less than 50% stenosis by diameter. If such individuals develop a minor fissure over which a large thrombus develops which is subsequently lysed an angiographic appearance results which may be interpreted as normal. This process probably explains an unknown proportion of patients in whom infarction occurs with apparently normal arteries and is an alternative explanation to spasm as the causative factor.[47–49]

Process of plaque fissuring

Plaque fissuring is not a recent dicovery; its importance, however, is only now being fully appreciated. Throughout the last 60 years there has been considerable interest in the acute changes in plaques that initiate thrombosis. In 1926, Benson found that thrombi in the coronary arteries arose on

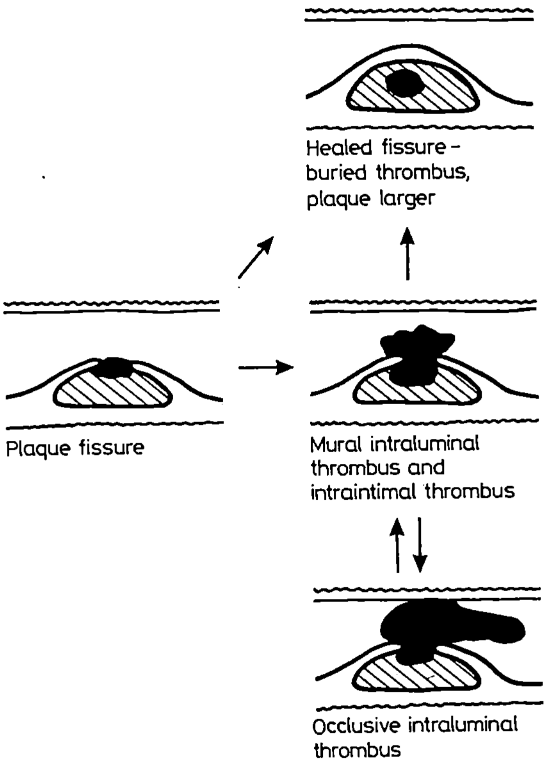
Healed fissure - buried thrombus, plaque larger
Plaque fissure
Mural intraluminal thrombus and intraintimal thrombus
Occlusive intraluminal thrombus

Fig. 8 *Diagrammatic representation of the evolution of a plaque fissure either to reseal and stabilise or to progress to thrombotic occlusion.*

the intima overlying plaques which had physically broken allowing, in his words, "dissecting haemorrhage from the lumen into the plaque."[50] Since that time many others have confirmed these lesions describing them as tears, breaks, ulcers, or ruptures of atheromatous plaques.[51,52] An early study of 32 coronary thrombi associated with myocardial infarction showed all to be related to "ulceration" of the plaque.[53] There was thus established the view that coronary thrombosis followed major physical disruption of the intima exposing lipid to the flowing blood. By disruption was meant gaps many micrometres or even millimetres in size demonstrable by conventional microscopy.

The basic principle was subsequently, and regrettably, undermined. Paterson described free red cells to be present within atheromatous plaques and ascribed this "haemorrhage" to bleeding from small vessels entering the intima from the media.[54,55] Paterson concluded that plaque haemorrhage was common and usually unassociated with overlying thrombosis. Argument raged over whether bleeding from such transmedial vessels could cause plaque growth sufficient to occlude the lumen but, in general, it was thought that intraluminal pressure would limit the bleeding. To many authorities in the field,[56] the work of Constantinides had finally re-established the importance of fissures from the lumen.[57] In 17 thrombi causing acute myocardial infarction reconstructed from serial sections cracks or fissures were found and "haemorrhage" in the plaque could be traced to an entry into the plaque from the lumen.[57] A view persisted, however, in the minds of some that fissures were "artefacts." This scepticism may be related to the ascendancy of the postulates of Duguid, who stated that fibrin within a plaque represented earlier surface thrombus incorporated into the intima.[58] This view of the growth of atheromatous plaques would be seriously weakened if it were to be accepted that intraplaque thrombus formation occurs via a fissure from the surface into the core of the plaque.

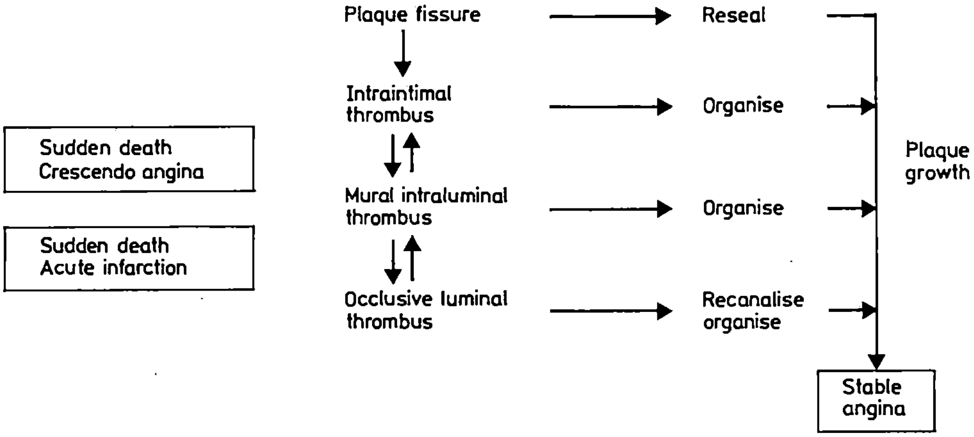

Fig. 9 *Relation between the clinical expressions of ischaemic heart disease and the stages of plaque fissuring.*

Conclusions

It can now be appreciated that there are two quite different processes encompassed by the term "plaque haemorrhage." The fact that the media behind plaques becomes intensely vascularised and that these vessels enter the intima is beyond dispute.[59 60] Bleeding from such vessels crossing the media causes a limited number of red cells to lie free within the lipid pool of many plaques. No fibrin or platelets are present, and the process is almost ubiquitous in large lipid rich plaques. The second process is the presence of large numbers of red cells, masses of platelets, and considerable amounts of fibrin within the plaque. If serial histological sections are used these elements can be traced to an entry into the lumen via a fissure, although this may be closed by a mass of thrombus. The two processes must be clearly separated and the term intraplaque thrombosis is more applicable to that associated with fissures from the lumen. It is plaque fissuring with related intraintimal thrombosis progressing to the formation of an intraluminal thrombus that is the important dynamic process unifying crescendo angina, acute myocardial infarction, and sudden ischaemic death.

It is difficult to escape the conclusion that the failure of pathologists to think in terms of dynamic processes and to believe what was seen at necropsy was an immutable reflection of events in life that occurred days before has seriously hindered the understanding by clinicians of how atheroma produces acute clinical symptoms.

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Mitral valve prolapse in hyperthyroidism of two different origins

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SUMMARY The prevalence of mitral valve prolapse was investigated in 126 patients with hyperthyroidism due to Graves' disease or toxic nodular goitre and that of hyperthyroidism in 64 patients with mitral valve prolapse. One hundred and eleven asymptomatic healthy subjects comprised a control group. The patients with hyperthyroidism were divided into those with Graves' disease and those with toxic nodular goitre. Of the group as whole, 12 (9·5%) patients had mitral valve prolapse compared with six (5·4%) in the control group, but the difference was not statistically significant. The prevalence of mitral valve prolapse in the patients with toxic goitre was also not significantly different from that in the controls. When the prevalence in the group with Graves' disease was compared with that in the control group (16·3% *vs* 5·4%) the difference was significant. Only one patient with mitral valve prolapse had hyperthyroidism.

Since the first description by Barlow in 1963 of mitral valve prolapse, numerous reports have been published.[1 2] The prevalence of the condition appears to be increasing partly owing to increased clinical awareness and partly to the increased use of echocardiography, and figures between 1% and 21% have been reported in otherwise normal populations.[3–6] Medical opinion of the clinical importance of mitral valve prolapse also varies. It ranges from being considered to have a poor prognosis owing to a high rate of arrhythmias and endocarditis[7 8] to being considered as a normal anatomical variation of the mitral valve apparatus.[9] Mitral valve prolapse has been reported associated with disorders such as Marfan's syndrome,[10] osteogenesis imperfecta,[11] and others.[12 13]

The prognosis is influenced by the causation of the mitral valve prolapse. Primary prolapse generally has a good prognosis while secondary prolapse, especially when due to occlusive coronary disease, is more serious.[14] Channick *et al* reported a very high incidence of mitral valve prolapse in patients with hyperthyroidism,[15] which is possibly related to increased adrenergic tone in both conditions. Our experience of large numbers of hyperthyroid patients did not indicate such a high prevalence. We therefore decided to investigate a large population drawn from our endocrine and cardiological institutes in order to determine the prevalence of hyperthyroidism in patients with mitral valve prolapse.

Patients and methods

Three groups of subjects were examined.

Group 1 consisted of 126 hyperthyroid patients, of whom 99 (78·6%) were women (age range 19–76 (mean 44·8) years) and 27 (21·4%) men (age range 28–78 (mean 49·6) years). Most of the patients were euthyroid at the time of examination as a result of various treatments, and only a few were still hyperthyroid. In this group 49 patients had Graves' disease based on a thyroid scan and the accepted clinical criteria of diffuse goitre and exophthalmos. Seventy seven patients had toxic nodular goitre. Patients with chronic or subacute thyroiditis were excluded.

Group 2 consisted of 111 asymptomatic subjects drawn from our inpatient and outpatient population, of whom 88 were women (age range 15–88 (mean 46) years) and 23 men (age range 16–75 (mean 50) years). The proportions of men and women in this group were similar to those in group 1, and none had any endocrine or cardiac abnormalities. This group con-

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Table 1 *Frequency of mitral valve prolapse in 126 patients with Graves' disease or toxic nodular goitre (group 1) and in controls (group 2)*

	No (%) of patients	*Women*		*Men*		*Total No (%) with MVP*
		No (%)	*Mean age (yr)*	*No (%)*	*Mean age (yr)*	
Group 1						
With Graves' disease	49 (38·9)	39 (79·6)	51·9	10 (20·4)	44·4	8 (16·3)
With toxic nodular goitre	77 (61·1)	61 (79·2)	53·3	16 (20·8)	51·6	4 (5·2)
Group 2	111 (100)	88 (97·3)	44·5	23 (20·7)	59·3	6 (5·4)

MVP, mitral valve prolapse.

stituted the control group, and in order to preclude any bias they were not examined for heart murmurs.

Group 3 consisted of 64 patients, of whom 32 were women (age range 18–62 (mean 28·5) years) and 32 men (age range 15–69 (mean 31·2) years) with both auscultatory and echocardiographic evidence of mitral valve prolapse.

All the subjects in the three groups underwent thyroid function tests (total thyroxine (TT4) by radioimmunoassay, T3 resin uptake, free thyroxine index and both M mode and cross sectional echocardiography, which were performed on a Smith Kline Echoline 20A echocardiograph with recordings made on a VR12 instrument in both the parasternal long axis and apical four chamber views. The echocardiograms were read by two experienced echocardiographers without prior knowledge of the diagnosis. The criteria for the diagnosis of mitral valve prolapse were mid systolic buckling or pansystolic hammocking >3 mm below the C-D line on the M mode echocardiogram and protrusion of the mitral leaflets beyond the plane of the atrioventricular ring in the long axis view and prolapse of the leaflets beyond the mitral annulus in the four chamber view on the cross sectional echocardiogram.

Statistical analysis was performed with the χ^2 test.

Results

Table 1 summarises the sex distribution of patients in groups 1 and 2. Group 1 was subdivided into those with Graves' disease (49 (38·9%) patients) and those with toxic nodular goitre (77 (61·1%) patients). The proportions of men and women were similar in the two subgroups. In the patients with Graves' disease 16·3% had mitral valve prolapse compared with only 5·2% of those with toxic nodular goitre. In group 2 (the control group), of 111 patients only six (5·4%) had mitral valve prolapse. Of 64 patients already known to have mitral valve prolapse (group 3) only one was biochemically hyperthyroid but with no clinical manifestations. In both groups 1 and 2 the prevalence of mitral valve prolapse was much higher in women (10/12 (83·4%) and 6/6 (100%) respectively).

Of the 12 hyperthyroid patients with mitral valve prolapse only one had a mid systolic click and a late systolic murmur. Four patients had a faint short systolic murmur which was considered to be functional, and five had neither a click nor a murmur. Some of the other patients in group 1 without prolapse had minor murmurs but no clicks.

Table 2 shows the thyroid function in group 1 at the time of examination; there was no difference in the occurrence of mitral valve prolapse in hyperthyroid or euthyroid patients (10·3% and 9·3% respectively). The frequency of mitral valve prolapse in patients with Graves' disease was significantly higher than in the controls ($\chi^2=4{\cdot}11$, $p<0{\cdot}05$). When the patients with Graves' disease were compared with those with toxic nodular goitre the difference was not significant ($\chi^2=3{\cdot}09$, $0{\cdot}1>p>0{\cdot}05$). Similarly the difference was not significant between the toxic nodular goitre group and the controls or between the hyperthyroid group as a whole and the controls.

Discussion

Channick *et al* surprisingly found a very high incidence of mitral valve prolapse in patients with hyperthyroidism due to Graves' disease (41% of 39

Table 2 *Thyroid function of 126 patients with hyperthyroidism (group 1)*

Thyroid state	*No (%) of patients*	*No (%) of women*	*No (%) of men*	*Total No (%) with MVP*
Hyperthyroid	30 (24·6)	25 (86·2)	5 (17·2)	3 (10·3)
Euthyroid	96 (75·4)	75 (77·3)	21 (21·6)	9 (9·3)

MVP, mitral valve prolapse.

patients).[15] One patient with toxic nodular goitre in this series also had mitral valve prolapse.[15] Until this report, the connection between Graves' disease and mitral valve prolapse was unknown.

Graves' disease and mitral valve prolapse have some similarities, which could point to a common denominator. Graves' disease is seven times more common among women. The ratio of women to men with mitral valve prolapse in reported series varies from 1·4 : 1 in one study[16] to 3 : 1 in another.[17] In our series 79·6% of the patients with Graves' disease were women, and mitral valve prolapse was found in a ratio of 4 : 1 in favour of women (Table 1).

Genetic factors have been identified in Graves' disease[18] and also in mitral valve prolapse. An incidence of mitral valve prolapse of 50% in monozygotic twins has been reported.[19 20] The condition was also found in identical twins.[21] The peak incidence of Graves' disease occurs during the third and fourth decades. Although seen in infancy,[22] mitral valve prolapse becomes more evident in adult life, possibly owing to progressive myxomatous degeneration of the mitral valve apparatus as a consequence of ischaemic heart disease, connective tissue abnormalities, or trauma.[1]

Graves' disease is known to be associated with the major histocompatibility antigens Bw35, DRw3, and B8.[23] In patients with mitral valve prolapse some studies showed a higher prevalence of HLA-Bw35 (73% *vs* 39% in controls), but only in American black subjects.[24] Another study of predominantly white patients showed that the A3; Bw35 phenotype is quite specific for mitral valve prolapse.[25] Nevertheless, in another study no HLA correlation was found in white subjects.[26] No ABO blood group specifity was found in American black subjects.[24] Autoimmunity is a well known causative factor in Graves' disease,[27] and recently it has been mentioned also in the aetiology of mitral valve prolapse. Miklozek *et al* and Schlant *et al* reported that 20 out of a total 40 patients with mitral valve prolapse had a positive antinuclear factor compared with only 4% in a matched control group.[28 29] Several manifestations usually seen in autoimmune connective tissue disorders (joint pains, rheumatic fever, hair loss, Raynaud's phenomenon, and pleuritis) were found in these patients.

For many years the cardiac manifestations of hyperthyroidism were thought to be mediated by catecholamines or hyperthyroidism to be associated with an increased adrenergic tone.[30] Aoki *et al* suggested that the cardiac effects of hyperthyroidism were due to the direct effect of thyroid hormones[31] rather than induced by catecholamine hypersensitivity. On the other hand, Boudoulas *et al* found increased catecholamine concentrations and higher adrenergic tone in patients with mitral valve prolapse.[32] In the present study the incidence of hyperthyroidism was negligible in a large group of patients with mitral valve prolapse, as found also by others.[33] Whatever the relation between these two disorders, therefore, it is probably not due to increased adrenergic tone.

In our study we confirmed the findings of Channick *et al*[15] of a higher prevalence of mitral valve prolapse in patients with Graves' disease. Although the number of patients that we examined was larger, the proportion of patients with mitral valve prolapse was smaller but still significantly larger than that in euthyroid controls. Moreover, mitral valve prolapse was no more frequent in patients with toxic nodular goitre than in the controls.

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Is a family history of coronary heart disease an independent coronary risk factor?

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SUMMARY The importance of a positive family history as a primary risk factor for coronary heart disease was examined in a case history study. Of 792 consecutive male patients aged under 60 years who survived a first episode of unstable angina or myocardial infarction, 326 had a negative family history, 298 had a positive history, and in 168 a family history could not be established with certainty. There was no significant difference in the distribution of the three primary coronary risk factors—cigarette smoking, hypertension, and hypercholesterolaemia—between those with and those without a positive family history. The 133 subjects with a positive family history of premature coronary heart disease (occurrence in near relatives under 60 years) were significantly younger than those with a negative family history.

It is concluded that there is little evidence to confirm a positive family history as an important independent risk factor for coronary heart disease, although there may be familial aggregation of subjects with a high susceptibility to the effects of the three primary risk factors, cigarette smoking, hypertension, and hyperlipidaemia.

Although a positive family history is widely accepted as an independent risk factor for coronary heart disease, there is little published evidence to support this view. It has been suggested that the aggregation of coronary disease in families can be attributed to the high prevalance of the condition in Western society and to family aggregation of coronary heart disease risk factors, including hyperlipidaemia, hypertension, obesity, smoking, and diabetes.

There are three ways in which a positive family history might be related to the development of coronary heart disease: (*a*) as an index of the inheritance of risk factors; (*b*) as a truly independent risk factor; and (*c*) as a vulnerability factor potentiating the action of risk factors.

Studies of familial aggregation of coronary heart disease are usually either case-control studies of its prevalence in the relatives of patients and of matched controls[1] or prospective studies at population level.[2] An alternative approach is to examine the risk factor profiles of patients with established coronary heart disease. If we take the occurrence of the first acute coronary event as marking a definable stage in the progress of the disease we may make specific predictions about the relation between family history and other risk factors in patients at this stage of disease progression.

If family history of coronary heart disease is simply an index of the inheritance of one or more risk factors, we would expect to find a different risk factor profile in patients with a positive history. If, on the other hand, a positive family history is an independent risk factor for coronary heart disease we would expect to find lower frequencies of other acknowledged risk factors among patients with a positive history than among those with a negative history. The third possibility is that family history acts as a potentiating factor to one or more risk factors—for example, by the genetic transmission of a tendency to narrow blood vessels. In this case, we would expect to see the same combination of risk factors in patients with and without a family history, but we would expect the former group to be younger at the time of their first acute episode.

The aim of this study was to examine the risk factor profiles of survivors of a first episode of unstable angina or myocardial infarction to determine whether

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they provided support for any of the models outlined above.

Patients and methods

Cases were drawn from the St Vincent's Hospital Heart Study. This is a long term follow up study of consecutive 28 day survivors of a first acute episode of coronary heart disease. Cohort 1 was recruited between 1965 and 1975 and cohort 2 between 1978 and 1983. The patients included in the present analysis were male and aged under 60 years and had survived a first episode of unstable angina or myocardial infarction by 28 days. Patients with unstable angina were included only if, in the presence of typical cardiac pain at rest, they had serial ST-T changes in the electrocardiogram with either no increase or a less than twofold increase in cardiac enzyme activities (creatine kinase, lactic dehydrogenase, and aspartate aminotransferase). Myocardial infarction was diagnosed on the basis of cardiac pain at rest with new Q waves in the electrocardiogram or at least a twofold rise in cardiac enzyme activities or both.

Family history of coronary heart disease was defined as one or more of the patient's parents or siblings having an acute episode of coronary heart disease or having angina of effort. Additional information on family history was available for patients in cohort 1 allowing a comparison to be made between patients without a family history and those of whom at least one parent or sibling under the age of 60 had had an acute event or angina of effort. Two analyses were therefore performed, one comparing patients without a family history with those with a positive history, the other comparing patients without a family history with those with a family history of premature coronary heart disease. In several instances the family history could not be rated confidently because of early parental death, loss of contact with family members, or similar reasons. Such patients were excluded from the study. Table 1 shows distribution of family history of coronary heart disease for the two analyses.

Other risk factors were defined as follows: cigarette smoking was rated as 0, for non-smokers; 1, for ex-smokers, and 2, for current smokers. An ex-smoker was defined as not having smoked for three months or more before the admitting episode. The relation of weight to height was calculated using Quetelet's body mass index, which is the ratio between the patient's weight (in kg) and his height squared (in m^2). Total serum cholesterol concentration was assayed from a blood sample usually taken within 12 hours of the onset of an attack. Hypertension was diagnosed in patients fulfilling at least one of the following criteria: (*a*) a diastolic blood pressure >90 mm Hg during hospital stay; (*b*) a diastolic blood pressure consistently >110 mm Hg measured at the outpatient clinic; (*c*) treatment for hypertension before the admitting episode, or (*d*) the presence of at least two of the following: a past history of hypertension, electrocardiographic evidence of left ventricular hypertrophy, or hypertensive retinopathy.

All the factors were examined individually for differences between family history groups and simultaneously by means of discriminant function analysis. A discriminant function produces the optimal combination of a number of measures for the purpose of discriminating between a number of subgroups.

Results

Risk factor data were available for 792 patients who fulfilled the entry criteria. These comprised 553 consecutive admissions between 1965 and 1975 inclusive (cohort 1) and 239 consecutive admissions between 1978 and 1982 inclusive (cohort 2). Table 1 shows the distribution of family history of coronary heart disease in the two cohorts. One hundred and sixty eight patients were unable to provide enough information for us to rate family history with certainty and were excluded from the analysis. Of the remaining 624, 326 (52%) had a negative family history.

Table 2 shows the distribution of the individual risk factors between the two family history groups. In the first analysis, in which subjects with a positive history were compared with those without, levels of individual risk factors were similar in both groups, with the exception of serum cholesterol concentration; the

Table 1 *Distribution of family history of coronary heart disease (CHD). Figures are numbers (%) of subjects*

Coronary heart disease	*Cohort 1*	*Cohort 2*	*Total*
Negative history	236 (42·7)†	90 (37·7)	326 (41·2)*
Doubtful history	135 (24·4)	33 (13·8)	168 (21·2)
History in parent or sibling:			
Aged ≥60	49 (8·9)	NA	
Aged <60	133 (24·0)†	NA	
Any age	182 (32·9)	116 (48·5)	298 (37·6)*
Total	553 (100)	239 (100)	792

NA, not applicable.
*Data compared in analysis 1.
†Data compared in analysis 2.

Table 2 *Distribution of risk factors in relation to negative or positive family history*

	Analysis 1†		*Analysis 2*‡	
	Negative	*Positive*	*Negative*	*Positive*
Number of cases	326	298	236	133
% of current smokers	71·8	65·1	75·4	70·7
% of patients with known hypertension	17·2	14·1	15·7	18·1
Mean cholesterol concentration (mg/100 ml)	244·6	253·4	252·1	260·5
Mean age (years)	50·9	50·2	51·2	49·5*
Mean body mass index	24·8	25·2	24·8	25·0

*Significant: $t=2·29$, df=252, $p=0·023$ (separate variance estimate); no other differences significant. χ^2 test (smoking, hypertension), and grouped *t* test (cholesterol, age, body mass index) used.
†All negative cases *vs* all positive cases.
‡Negative cases *vs* coronary heart disease in parent or sibling <60 years for cohort 1.
Conversion: traditional to SI units—cholesterol: 1 mg/100 ml≈0·026 mmol/l.

subjects without a family history had a cholesterol concentration 0·2 mmol/l (9 mg/100 ml) lower than those with a positive history. This difference was of borderline significance ($t=1·76$, $p=0·079$, separate variance estimate used). In the second analysis, in which subjects with a family history of premature disease (in a near relative under 60 years) were compared with those with no family history, the distribution of risk factors was again similar in both groups, but the mean age of those with a positive history was 1·7 years lower than that of subjects with a negative history ($p=0·023$). No difference in mean cholesterol concentration was found between the two groups.

Attempts to find a characteristic risk factor profile that distinguished subjects with a positive family history from those without, using discriminant function analysis, were unsuccessful. Using age, cholesterol concentration, body mass index, smoking status, and hypertension, stepwise functions were calculated. The optimal combination of these factors explained only 1·75% of variance between positive and negative family history groups. When subjects with a negative history were compared with those with a history of premature coronary heart disease, the percentage of variance explained rose to 2·16%, but the function was only able to classify subjects into the appropriate family history groups with 55% accuracy—that is, 5% better than chance expectancy.

In addition, we examined the risk factors of the subjects in whom a firm rating of family history could not be made. They did not differ significantly from other subjects in any of the factors studied.

Discussion

There is a well established aggregation of coronary risk factors and of cases of coronary heart disease in families.[3 4] This may be attributed to the frequency of the condition in Western society, to a shared family environment, to a genetic susceptibility to the effects of individual risk factors, to a greater predispostion to individual risk factors, to a primary genetic predisposition to atherosclerosis, or to a combination of two or more of these factors. The concept of a genetic predisposition has occupied the minds of previous authors, but no agreement has been reached about the importance of family history as a primary risk factor.

Epstein, in earlier reviews, states that there is little support for the unqualified statement that "the family history is important" in predicting the risk of coronary heart disease in the individual.[5 6] He does imply, however, that the clustering of hyperlipidaemia and hypertension in families is not sufficient to account for the entire aggregation of cases of coronary heart disease within families. The clustering of known or unknown risk factors, including cigarette smoking, diabetes, and obesity, may possibly contribute further to family aggregation.

McKusick, in an earlier review, states that among the few twin studies of clinical coronary heart disease, the majority are consistent with the hypothesis of an important genetic factor.[7] He quotes studies of monozygotic twins living together and apart, which would support the influence of both environmental and genetic factors.

The Western Collaborative Study reported that a positive family history was independently predictive of coronary heart disease only in men aged less than 50 years.[8] In the Paris Prospective Study of 7484 men it was found that a paternal, but not a maternal, history was independently predictive of coronary heart disease.[9] In a study of 186 pairs of brothers in Framingham coronary heart disease in an older brother was predictive of both non-fatal and fatal myocardial infarction in the younger sibling, after controlling for cholesterol concentration, cigarette smoking, and hypertension.[10]

Ten Kate *et al* report a case control study of 145 male survivors of myocardial infarction matched with 145 apparently healthy male blood donors and compared with an equal number of first degree relatives of both groups.[1] They conclude that family aggregation of coronary heart disease is not entirely explained by clustering of known risk factors. They state that such an aggregation could be caused by undefined genetic factors, by environmental factors, or by a combination of both.

In a recent study involving a nine year follow up of 4014 healthy men and women, Barrett-Connor and Khaw found that men under 60 years with a positive family history had higher mean blood pressure and plasma cholesterol concentrations than those with a negative history, while older men with a positive history had a higher incidence of diabetes.[2] Young women with a positive family history were more likely to smoke cigarettes and older women to have taken exogenous oestrogens. They found that, in younger men only, a positive family history was independently predictive of death from cardiovascular and all causes but not from coronary heart disease. On the other hand, a prospective study of 4050 men in Finland failed to show any association between family history of premature coronary heart disease (under age 50) and risk of either stroke or myocardial infarction[11] when other risk factors were controlled for.

Our own results fail to elucidate the problem, but they do not support the hypothesis of a genetic influence as an independent risk factor. The non-significant but higher cholesterol concentrations in our patients with a positive family history do not exclude the possibility of a subgroup of patients with a genetic tendency to hyperlipidaemia, and the younger age of patients with a positive family history of premature disease is consistent with an inherited susceptibility to the action of coronary risk factors. Our results, however, like those of previous studies, serve mainly to emphasise the uncertainties that still exist about the importance of a family history and to point to the need for further research into this area. It is possible that a definitive answer may not be found to the question because of the difficulties inherent in studies of this type, in which a primary risk factor must be distinguished from a genetic tendency to acknowledged risk factors, an increased susceptibility in some families to the effect of such risk factors, and the shared environmental influences that exist within families. The situation may be compounded further by the probability that two or more of these factors may be operative and by the fact that the family history status may change with the development of new cases of coronary heart disease in family members.

Perhaps the only, and certainly the most important, conclusion that can be drawn from our study of a large group of patients and from previous studies is that a positive family history is not an independent primary risk factor of the same magnitude as hyperlipidaemia, hypertension, or smoking. This is supported by the results of migration studies and by our own study of risk factors in 757 male patients under 60 years with a first myocardial infarction.[12] Only 14 of these patients were free of the three primary risk factors (never smoked cigarettes, had normal blood pressure, and had a serum cholesterol concentration <6·2 mmol/l (240 mg/100 ml). Of these 14, seven had a negative family history, three had a positive history, and in the remaining four the patient could not give sufficient information to make a rating with certainty.

Patients with a family history of coronary heart disease—if they are free of the acknowledged risk factors of cigarette smoking, hypertension, and hyperlipidaemia—can, we believe, in the context of current knowledge, be reassured about their risk of developing clinical coronary heart disease.

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Family history of myocardial infarction as an independent risk factor for coronary heart disease

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SUMMARY The hypothesis that a family history of heart attack before the age of 60 years is an independent risk factor for coronary heart disease was examined in a random sample of 1044 men aged 40–70. Data on personal and family history, smoking, weight, height, plasma lipid and lipoprotein concentrations, blood pressure, and resting and exercise electrocardiograms were collected according to the standard Lipid Research Clinics protocol. A history of heart attack in first degree relatives was ascertained by interviewing the participants. Evidence of coronary heart disease was found in 123 men (reported heart attack in 20, electrocardiographic findings of ischaemic heart disease at rest in 40, and electrocardiographic findings during heart rate limited exercise in 63). Subjects with coronary heart disease had considerably higher concentrations of total cholesterol, higher blood pressures, and lower concentrations of high density lipoprotein cholesterol than those without. Twenty nine per cent of the subjects with coronary heart disease reported a history of heart attack in a first degree relative before 60 years of age compared with 19% of those without. In a multivariate logistic model, the coefficients for age, cholesterol concentrations, and hypertension were all positive and statistically significant. The coefficient for HDL cholesterol concentration was negative and significant. A family history of heart attack showed a significant positive association, indicating a relation with coronary heart disease that is independent of the other variables in the model. The relation persisted in apparently asymptomatic patients with coronary heart disease.

There is ample evidence that coronary heart disease tends to cluster in families.[1–4] The major documented risk factors for the development of coronary heart disease have important genetic determinants.[5–8] They may account for most of the familial aggregation of coronary heart disease.[9–11] The question arises whether the aggregation of coronary heart disease is due to factors other than the familial aggregation of the established coronary heart disease risk factors. A family history of heart attack or coronary heart disease was shown to be a strong predictor of coronary heart disease even after adjustment for other risk factors.[12] The present report includes data from the Jerusalem Lipid Research Clinic Prevalence Study.[13] The objective of the present study was to evaluate the association of a history of heart attack before the age of 60 years in first degree relatives with the prevalence of coronary heart disease in study participants and to test the hypothesis that this association is independent of other risk factors.

Subjects and methods

STUDY POPULATION

The basic design of the Jerusalem Lipid Research Clinic has been described in detail.[13] At the preliminary examination 8646 boys and girls, aged 17 years, were interviewed at their military induction health examination. A 56% random sample of their parents were also invited to attend; these subjects formed the basis of the study group. At this visit sociodemographic information and data on the reported use of medications were collected and fasting plasma cholesterol, triglyceride, and high density lipoprotein (HDL) cholesterol concentrations were measured. Of

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the total of 6952 parents who were examined at the first visit, a random sample of 44% of the fathers and 20% of the mothers were invited for a second more extensive examination. The attendance rates were 72·0% and 79·7% at the two examinations. At the second visit detailed information on the use of medications, diet during the 24 hour period before examination, alcohol consumption, and cigarette smoking as well as medical and family history were recorded according to the standardised Lipid Research Clinics protocol.[14] The examination included determination of plasma cholesterol, triglyceride, and lipoprotein cholesterol concentrations, including low density lipoprotein (LDL) and HDL cholesterol, blood pressure and anthropometric measurements, and a resting and exercise electrocardiogram. Blood pressure was measured four consecutive times using the conventional mercury sphygmomanometer for the first and third measurements and a zero muddler device for the second and fourth. Blood pressure was measured on the right arm with the subject seated. The systolic and the fifth phase diastolic pressures were recorded. For this analysis the mean of the two standard readings was used. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg or the use of antihypertensive medication by the subject. The Quetelet index (weight/height^2) was used as a measure of body mass.

FAMILY HISTORY

At the second visit, data on the subjects' family health history were collected by a trained interviewer using the Lipid Research Clinics standardised questionnaire.[14] A series of questions provided information on the occurrence of myocardial infarction or angina pectoris before the age of 60 years in fathers, mothers, siblings, and children. For the present analysis a positive family history of myocardial infarction was defined as the occurrence of myocardial infarction before 60 years of age in one or more first degree relatives of the subject. The information obtained about the family health history was not validated against hospital or family doctor records.

RESTING ELECTROCARDIOGRAM

During the second visit each subject had a resting 12 lead electrocardiogram recorded in the supine position by technicians trained in the standardised performance of the procedure. Electrocardiograms were recorded on both paper and magnetic tape and sent for interpretation to the projects' central electrocardiographic laboratory in Birmingham, Alabama, USA. Electrocardiograms were read by computer as well as by two independent coders according to the Minnesota Code.[15]

EXERCISE ELECTROCARDIOGRAM

Submaximal exercise testing using an age specific target heart rate was performed according to the modified Bruce protocol.[16] Before the exercise test a doctor took a medical history and performed a physical examination. Based on this evaluation subjects were either considered to be eligible for the treadmill test or excluded from the study. Subjects started walking on the treadmill at 1·7 mph on a 10% gradient for the first three minutes. The speed and the slope were increased every three minutes until the subject reached 85–90% of his age adjusted predicted maximum heart rate. Tests were terminated prematurely because of fatigue or medical contraindication to continued exercise. Heart rate and blood pressure were recorded at the end of each three minute stage of exercise and at 0, 2, 4, and 6 minutes after exercise. A six lead (V4, V5, V6, X, Y, and Z) electrocardiogram was recorded during and after the exercise at the same times as above.

CRITERIA FOR CORONARY HEART DISEASE

Subjects were considered to have coronary heart disease if they (*a*) reported an admission to hospital because of a heart attack, (*b*) had resting ischaemic electrocardiographic abnormalities (including major and minor Q wave abnormalities (Minnesota codes 1.1.1–1.1.7; 1.2.1–2.8; 1.3.1–3.6), major ST depression (4.1; 4.2), and major T wave abnormalities (5.1; 5.2), and (*c*) had positive ischaemic electrocardiographic findings on the treadmill. The exercise test was defined as positive if ST segment depression during or after exercise exceeded 1 mm as measured by trained coders or a 10 mV/s fall in ST integral from its resting value assessed by a computer coding system. Hypotension and development of angina on the treadmill were also criteria for a positive exercise test.[14]

STATISTICAL ANALYSIS

Univariate and multivariate analyses were performed by a linear logistic regression model. This procedure models the disease status (that is, the prevalence of coronary heart disease) as an exponential function of a linear combination of the risk factors. Under each model the predicted probability of coronary heart disease as a function of n independent variables was estimated by:

$$P(CHD)=\exp\,(b_o+\sum_{i=1}^{n} b_i\,X_i)/(1+\exp\,(b_o+\sum_{i=1}^{n} b_i\,X_i))$$

The regression coefficients were computed using the Walker-Duncan maximum likelihood procedure.[17] The statistical significance of coefficients in the model was tested by dividing the coefficients by their standard errors. The estimated regression coefficients for a risk factor expressed as a dummy variable or the

Table 1 *Mean (SD) plasma lipid and lipoprotein concentrations, body mass index, and prevalence of hypertension, smoking, and family history of heart attack among male subjects with and without coronary heart disease (CHD)*

	With CHD (n=123)	*Without CHD (n=921)*
Age (yr)	52·1 (7·0)	49·8 (6·4)
Total cholesterol (mg/100 ml)	212·8 (40·6)	201·3 (37·6)
LDL cholesterol (mg/100 ml)	138·8 (35·2)	128·6 (32·5)
HDL cholesterol (mg/100 ml)	38·8 (8·3)	41·0 (10·4)
Triglyceride (mg/100 ml)	172·2 (73·5)	161·1 (100·7)
Body mass index (weight/height^2)	2·68 (0·39)	2·63 (0·34)
% of patients:		
Smoking	30·9	40·0
With hypertension	43·9	27·6
With family history of heart attack	28·5	19·1

LDL, low density lipoprotein; HDL, high density lipoprotein.
Conversion: traditional to SI units—cholesterol: 1 mg/100 ml≈0·03 mmol/l; triglyceride: 1 mg/100 ml≈0·01 mmol/l.

standardised coefficients for continuous variables, when exponentiated, yield an estimate of the odds ratio.

Results

The study population included 1044 men aged 40–70 years from the second visit random recall group. Of these, 20 reported a previous heart attack, 40 had ischaemic resting electrocardiogram abnormalities, and 63 developed ischaemic electrocardiographic findings during the exercise test. Table 1 summarises the characteristics of the 123 subjects with (study group) and the 921 subjects without (control group) coronary heart disease. The mean age of those subjects with coronary heart disease was two years higher than that of those without. The study group had higher mean values of total cholesterol and LDL cholesterol and lower mean values of HDL cholesterol than the control group. There was no overt difference in body mass index between the two groups. Of the study and control groups, 31% and 40% respectively were current smokers and 29% and 24% respectively were ex-smokers. The prevalence of hypertension was higher in the study group (44%) than in the control group (28%). A greater proportion of the study group reported a history of heart attack in a first degree relative (29%) than of the control group (19%).

Table 2 shows the results of logistic modelling with a set of risk factors. In the univariate analysis, age, total cholesterol and HDL cholesterol concentrations, and hypertension were statistically significant predictors of coronary heart disease. As expected, age, total cholesterol concentrations, and hypertension were positive correlates whereas HDL cholesterol concentration was inversely associated with coronary heart disease. Smoking showed an inverse association (not statistically significant) and body mass index a weak and not statistically significant correlation with disease prevalence in our sample. In the multivariate analysis the negative association with HDL cholesterol was strengthened. The multivariate coefficient for hypertension was smaller than the univariate coefficient, probably owing to the adjustment for age and body mass. The association with smoking was unchanged and that with body mass eliminated. The χ^2 associated with the likelihood ratios was higher for the multivariate model, which included total cholesterol, than the χ^2 for the model with LDL cholesterol. We therefore preferred the model with total cholesterol, although this did not significantly increase prediction.

Table 3 shows the logistic coefficient and the relative odds with its 95% confidence interval for family

Table 2 *Logistic regression models for coronary heart disease (CHD) in 123 subjects with and 921 without coronary heart disease as a function of age, total plasma cholesterol and high density lipoprotein (HDL) cholesterol concentrations, smoking, hypertension, and body mass index*

Independent variables	*Univariate model*			*Multivariate model*		
	Regression coefficient	*Odds ratio*	*CI†*	*Regression coefficient*	*Odds ratio*	*CI†*
Age	0·051**	1·39	1·17–1·66	0·048**	1·36	1·14–1·65
Total cholesterol	0·008**	1·34	1·12–1·61	0·007**	1·32	1·09–1·59
HDL cholesterol	−0·022*	0·79	0·65–0·97	−0·032**	0·72	0·58–0·90
Smoking	−0·399	0·67	0·44–1·02	−0·410	0·66	0·44–1·01
Hypertension	0·721**	2·06	1·37–3·09	0·481*	1·62	1·07–2·41
Body mass index	1·080	1·14	0·95–1·37	0·064	1·02	0·84–1·25

*p<0·05; **p<0·01;
†95% confidence interval for the odds ratio.

Table 3 *Logistic regression coefficients for family history of heart attack in all 123 subjects with and 921 without coronary heart disease (CHD) and separately in 48 asymptomatic subjects with and 921 without CHD*

	Univariate model			*Multivariate model*†		
	Regression coefficient	*Odds ratio*	*CI*‡	*Regression coefficient*	*Odds ratio*	*CI*‡
Total group	0·521*	1·68	1·09–2·60	0·491*	1·63	1·06–2·52
Asymptomatic group§	1·020	2·78	1·51–5·09	1·00**	2·72	1·48–4·99

*p<0·05; **p<0·01;.

†Age, cholesterol, HDL cholesterol, smoking, hypertension, and body mass index were included in the model in addition to family history variable.

‡95% confidence interval for the odds ratio.

§A positive exercise test without any other symptoms of CHD.

history of heart attack as a predictor of coronary heart disease. Based on the total study group the estimated odds of coronary heart disease being present in a subject with a family history of heart attack among his first degree relatives was 1·63 times that of a subject without this hisory when all other risk factors are controlled for. The 95% confidence interval for the odds ratio ranged from 1·06 to 2·52.

Prevalence studies may be subject to a number of well described biases. Our data allowed us to examine the possibility of bias resulting from a difference in recall of family history in subjects with and without coronary heart disease. Subjects with coronary heart disease who are aware of their condition may tend to over-report a family history of heart attack, and this could strengthen the association between family history and the disease. Subjects with asymptomatic coronary heart disease should be free of this potential bias. Thus all subjects with a history of heart attack and resting electrocardiographic abnormalities or those with a clinical picture of angina pectoris were excluded from analysis. The inclusion only of subjects with positive ischaemic electrocardiographic findings on the exercise test may produce a subgroup of coronary heart disease patients who are less likely to be aware of their medical condition. In this subgroup the positive association between family history and coronary heart diseasee was further strengthened (Table 3).

The odds ratio exceeded 2·7 both in the univariate and the multivariate model, with a 95% confidence interval ranging from 1·48 to 4·99.

Discussion

The findings in our study that total plasma cholesterol and HDL cholesterol concentrations and hypertension are statistically significant correlates of coronary heart disease are consistent with the findings of numerous other epidemilogical studies.

In the univariate analysis, heart attack before the age of 60 in first degree relatives was a significant predictor of coronary heart disease. With multivariate analysis the family history maintained its predictive strength in the presence of the other risk factors.

The mean ages of the subjects with and without coronary heart disease were 52 and 50 years respectively, with very few subjects aged under 40. Consequently, nearly all the parents of our study population were over 60 years old at the time of the study. Thus all had an equal probability of developing myocardial infarction before the age of 60. The mean number of siblings was similar in both groups (5·1 in study group and 5·0 in controls), but no data on the siblings' age and birth order were collected. We reran two logistic models, one using only parental history of myocardial infarction and the second only sibling history of myocardial infarction. The logistic coefficients were similar for both models, though they were somewhat stronger for that using sibling history. Small differences in the age distribution of siblings due to differences in the age of the study group and controls should be adequately controlled for by age adjustment in the logistic model. This assumption would be incorrect, however, if birth order or family spacing were determinants of coronary heart disease. The higher odds associated with sibling history than parental history indicate an increased risk associated with a history of heart attack in first degree relatives when the condition presented early in life.

The introduction of the family history variable as the last term in the stepwise logistic regression model did not alter the coefficients for the risk factors in the model. This indicates that the risk associated with family history is independent of the other major risk factors. This does not, however, imply lack of a familial pattern in the values for total cholesterol or HDL cholesterol or blood pressure in our data.[18] What this does appear to mean is that familial aggregation of these risk factors accounted for only a small part of the clustering of coronary heart disease in families. This clustering would therefore appear to reflect characteristics other than the classic risk factors that were measured in our study. These findings that the aggregation of coronary heart disease is not entirely explained by familial patterns in the different risk factors are consistent with other studies.[19-21] Nevertheless, at least one report appeared fully to explain the clustering of coronary heart disease among relatives by the familial aggregation of the documented risk factor.[11] We are unable to assess the relative importance of heredity and environmental factors in the association of family history with coronary heart disease. The contribution of heredity to the familial aggregation of ischaemic heart disease may be dominant.[22] Nevertheless, environmental factors such as diet (independent of lipid concentrations) and psychosocial factors that are shared by family members could contribute independently or interact with the heredity factor.

Several possible problems in our study need to be considered. Firstly, there was no verification of the reported family history, and therefore the validity of these data cannot be confirmed. Other studies such as the Tecumseh Community Health Study and the Tromsø Heart Study reported satisfactory validity of reported family history of heart attack.[19 23] There are no published data in Israel relating to this question. Secondly with prevalence data the possibility exists of bias due to factors such as selective survival, change in behaviour, and recall bias. For instance, in this study the proportion of current smokers among the study group was lower (31%) than among the control group (40%), although smoking has been shown to be a risk factor for myocardial infarction in Israeli men in a large prospective study.[24] Selective survival and recall bias could affect the association of family history with coronary heart disease. In particular, subjects with coronary heart disease may over-report a family history of heart attack. Biased recall, however, is unlikely to be responsible for our family history findings. Restricting the analysis to (probably) asymptomatic subjects did not weaken the association. The exercise electrocardiogram in asymptomatic subjects is known to be of relatively low specificity and small predictive value. Such misclassification would tend to reduce the odds ratio estimates towards the null value assuming that there is no differential misclassification of subjects with and without a positive family history. Thus our findings of a statistically significant association of coronary heart disease with a positive family history is probably an underestimate of the true association.

Our data suggest that a family history of myocardial infarction may be an important independent risk factor for the development of coronary heart disease in Israeli men. Further studies are needed to substantiate this finding and to explore the nature of this familial risk factor and the mechanism by which it produces coronary heart disease in our population.

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Effect of timolol on changes in serum potassium concentration during acute myocardial infarction

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SUMMARY One hundred and six patients with acute myocardial infarction admitted to hospital within four hours after the onset of symptoms were randomised to treatment with intravenous timolol (54 patients) or placebo (52 patients). Serum potassium concentrations were estimated at frequent intervals during the first 24 hours of admission. Patients in both treatment groups, who did not receive subsequent diuretic treatment, had a transient rise in serum potassium concentration, which was maximal after four hours. This rise was abolished by diuretic treatment in the placebo group but not in the timolol group, in which there was a pronounced and prolonged rise in serum potassium concentration. The change in serum potassium concentration in the first four hours after admission correlated with cumulative creatine kinase release in the placebo group, but not in the timolol group. Hypokalaemia (serum potassium concentration ≤3·5 mmol/l) occurred in 15 (28·8%) patients in the placebo group and in seven (13%) in the timolol group and was independent of infarct size. The frequency of hyperkalaemia was not increased in the timolol group.

By increasing the serum potassium concentration and preventing hypokalaemia, the use of intravenous timolol early in acute myocardial infarction may have important clinical effects in addition to reducing infarct size.

Low serum potassium concentrations have been associated with an increased frequency of cardiac arrhythmias in acute myocardial infarction,[1-3] and an inverse relation has been shown between serum potassium concentrations <5·2 mmol/l and the occurrence of ventricular fibrillation.[3] If the electrophysiological consequences of a low serum potassium concentration[4] are the cause of the increased frequency of arrhythmias, then prevention of hypokalaemia in the early phase of acute myocardial infarction, when arrhythmias are most frequent,[3] may be of importance. Serum potassium concentrations correlate inversely with catecholamine concentration,[5] which is increased in acute myocardial infarction,[6] and beta blocking drugs impair the potassium response to infused catecholamines in dogs[7] and healthy volunteers.[8] A small rise in serum potassium concentration has been reported in hypertensive patients treated with beta blockers.[9] Intravenous treatment with beta blockers has been shown to have beneficial effects on infarct size in acute myocardial infarction.[10-12]

The present study was undertaken to examine the effects of intravenous beta blockade with timolol maleate on serum potassium concentration and to determine the incidence of hypokalaemia during the first 24 hours after hospital admission in patients with acute myocardial infarction.

Patients and methods

The study population was a cohort from a randomised, double blind placebo controlled study of the nonselective beta receptor blocking drug timolol maleate in acute myocardial infarction.[10] The complete study included 144 patients, of whom 106 with definite infarcts are reported here. Thirty eight patients were excluded because of protocol violation, incomplete data, death within the study period, or unconfirmed infarction. The protocol for the study and the demog-

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raphic data of the patients have been fully reported previously.[10]

The patients were randomly allocated to intravenous treatment with timolol maleate or placebo. Treatment was started within five hours after the onset of symptoms with the injection of 1 mg of timolol or an equivalent volume of saline, and this was repeated 10 minutes later. After a further 10 minutes a constant infusion of timolol, 0·6 mg/hour, or an equal volume of normal saline was started and continued for 24 hours. Drugs, other than diuretics, known to affect the concentration of serum potassium were not used. Blood samples for measuring serum potassium concentration and creatine kinase activity were collected before the start of treatment with placebo or timolol, after two and four hours, and thereafter every four hours for the first 24 hours. The blood samples were immediately centrifuged and the serum frozen until the analyses were performed. Serum potassium concentration was analysed using flame photometry and creatine kinase concentration and cumulative release of creatine kinase as previously described.[10] Hypokalaemia was defined as a serum potassium concentration of ≤3·5 mmol/l and hyperkalaemia as a concentration of ≥5·2 mmol/l.

STATISTICAL ANALYSIS

Statistical tests were two tailed and p values <0·05 were considered to be significant. Student's *t* test was used to compare mean serum potassium concentrations between the treatment groups at comparable time intervals (unpaired *t* test) and also for comparing serum potassium concentrations before treatment with potassium values at subsequent time intervals within each treatment group (paired *t* test). Fisher's exact test was used to analyse categorical data. Linear regression analysis was used to correlate cumulative creatine kinase release and change in serum potassium concentration. Results are expressed as mean (standard error of the mean).

Results

Of the 106 patients in this study, 54 received timolol and 52 placebo. Data are given for all the patients together in each treatment group and according to whether or not diuretic treatment was given. In the timolol group 20 (37%) patients received a diuretic before the start of treatment or during the first 24 hours of the study; of these, 18 received frusemide (mean dose 63·6 (31) mg) and two thiazides. Twenty one (40%) patients in the placebo group received diuretics, of whom 19 received frusemide (mean dose 50·5 (18·1) mg) and two thiazides. The difference between the mean doses of frusemide in the two treatment groups was not significant.

Two patients in each treatment group also received oral potassium chloride supplements (placebo group 11 g and 6 g; timolol group 4 g and 1 g).

SERUM POTASSIUM CONCENTRATIONS

The mean serum potassium concentrations before treatment were comparable in the two groups; placebo 4·12 (0·07) mmol/l and timolol 3·99 (0·08) mmol/l. The mean time from the onset of symptoms of infarction to the start of treatment was 3·7 hours (placebo group) and 3·3 hours (timolol group) (NS). In the timolol group serum potassium concentrations rose to a significantly higher value compared with in the placebo group between four and 12 hours after the start of treatment. Patients treated with timolol had significantly higher serum potassium concentrations at 2, 4, 8, 12, 16, and 20 hours compared with before treatment. No such difference was seen in the placebo group (Fig. 1a).

In the patients not treated with diuretics before or

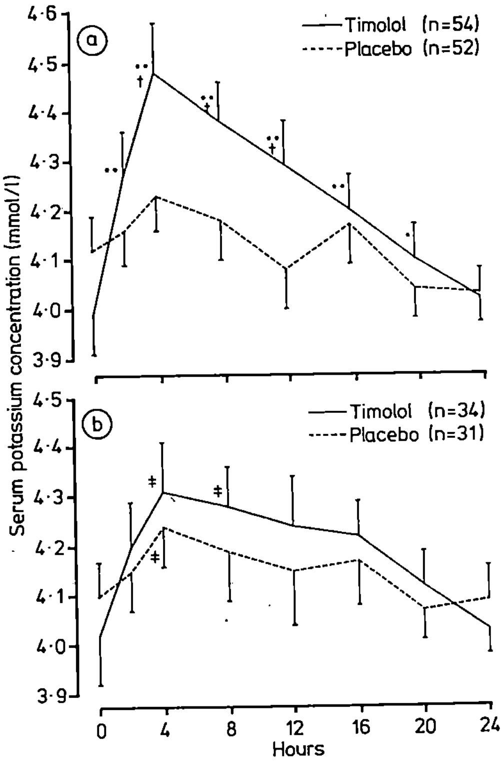

Fig. 1 *Mean (SEM) serum potassium concentration during 0–24 hours of drug administration in (a) all patients and (b) patients not treated with diuretics either on admission or during the first 24 hours. *p<0·05; **p<0·01 comparison with baseline; †p<0·05 comparison between timolol and placebo groups; ‡p<0·05 each time interval compared with baseline.*

Table 1 *Mean serum potassium concentrations (mmol/l) for patients treated with intravenous frusemide on admission and during the first 24 hours. Values are mean (SEM)*

Treatment group	*Before treatment*	*After treatment (hours)*				
		2	*4*	*8*	*12*	*24*
Placebo (n=15)	4·22 (0·17)	4·05 (0·14)	4·11 (0·2)	4·08 (0·14)	3·97 (0·15)*	3·89 (0·1)*
Timolol (n=12)	3·71 (0·17)	4·12 (0·2)*	4·63 (0·25)*	4·29 (0·18)*	3·93 (0·14)	3·95 (0·2)

*p<0·05 within group comparison with pretreatment values.

during the first 24 hours there was a significant increase from pretreatment values in mean serum potassium concentration in the placebo group at four hours and in the timolol group at four and eight hours (Fig. 1b). The increase was greatest in the timolol group, but there was no significant difference between the placebo and timolol group at any time. The probability of a difference between treatment groups between two and 24 hours was 0·16 by repeated measures analysis of variance.

The mean serum potassium concentration fell in patients in the placebo group who were treated with intravenous frusemide on admission and during the first 24 hours of the study. Compared with pretreatment values serum potassium concentration rose significantly at two hours in the patients in the timolol group who received frusemide (Table 1). The mean frusemide dosage was identical in the two treatment groups on admission and during the study. The mean cumulative creatine kinase release for these patients was 2290 (406) U/l in the placebo and 2121 (407) U/l in the timolol group (NS).

HYPOKALAEMIA

Timolol significantly reduced the incidence of hypokalaemia during the first 24 hours of treatment. During 2–24 hours after the start of treatment, 15 patients became hypokalaemic with placebo treatment, with a total of 35 hypokalaemic samples, compared with seven treated with timolol, with a total of 18 samples (Table 2). Hypokalaemia occurred more often in patients treated with diuretics in both groups (Table 2), but the lower overall incidence of hypokalaemia was not related to the administration of diuretics (Table 2). The lowest serum potassium concentration was 2·7 mmol/l. Hypokalaemia was transient, and only one patient had hypokalaemia in five consecutive samples during the 24 hour sampling period. In most patients with hypokalaemia this was noted in at most two or three consecutive samples (a duration of 6–12 hours).

Fourteen of 106 (13·2%) patients were hypokalaemic before treatment, three in the placebo and 11 in the timolol group. Only two of the 14 hypokalaemic patients had been treated with diuretics before admission. Of the 11 patients in the timolol group who were hypokalaemic before treatment, four had hypokalaemia at least once during treatment compared with one of three patients in the placebo group.

HYPERKALAEMIA

Six patients in the placebo and 10 in the timolol group had one or more hyperkalaemic samples during the study period (NS). Hyperkalaemia was transient; one patient in each group had four consecutive high serum potassium values, and one patient in each group had three consecutive high values. The highest value of serum potassium was 6·95 mmol/l. The incidence of hyperkalaemia before treatment was six of 106 (5·7%) patients (three in each treatment group), none of the values being ≥6·0 mmol/l. The number of patients with serum potassium values ≥6·0 mmol/l with treatment were three (5·8%) in the placebo and three (5·6%) in the timolol group.

CUMULATIVE CREATINE KINASE RELEASE AND SERUM POTASSIUM CONCENTRATION

The change in serum potassium concentration before treatment and at four hours (corresponding to the mean peak rise) in each patient not treated with intravenous frusemide was related to infarct size as estimated by cumulative creatine kinase release (Fig. 2). There was a significant correlation in both treatment groups, but a weaker correlation was obtained in the timolol group.

The mean cumulative creatine kinase release for

Table 2 *Patients with hypokalaemia (serum potassium concentration ≤3·5 mmol/l) on one or more occasions during the first 2–24 hours of timolol or placebo administration. Figures are numbers (percentages) of patients*

	Placebo	*Timolol*	*p value*
All patients	52	54	
With hypokalaemia at:			
2 hours	7 (13·5)	2 (3·7)	NS
2–4 hours	8 (15·4)	3 (5·6)	NS
2–8 hours	9 (17·3)	3 (5·6)	<0·05
2–24 hours	15 (28·8)	7 (13)	<0·05
Patients taking diuretics	21	20	
With hypokalaemia at 2–24 hours	8 (38·1)	4 (20)	NS
Patients not taking diuretics	31	34	
With hypokalaemia at 2–24 hours	7 (22·2)	3 (8·8)	NS

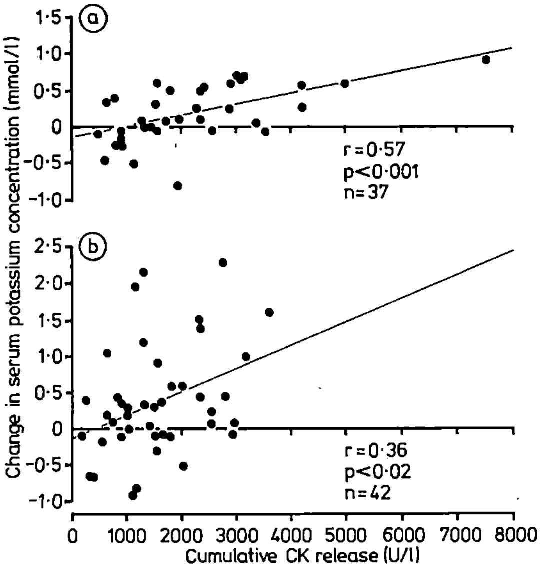

Fig. 2 *Change in serum potassium concentration from before treatment to four hours after treatment in relation to cumulative creatine kinase (CK) release in (a) placebo and (b) timolol patients not treated with diuretics.*

patients not treated with diuretics (Fig. 2) was 2056 (199) U/l in the placebo and 1323 (128) U/l in the timolol group ($p<0{\cdot}01$). The mean cumulative creatine kinase release for patients treated with diuretics was 2571 (415) U/l in the placebo and 2181 (264) U/l in the timolol group (NS).

In Table 3 cumulative creatine kinase release is related to potassium concentration. Infarct size was not significantly different between hypokalaemic patients and patients with serum potassium concentrations ≥3·6 mmol/l.

Discussion

This study has shown that early intervention with timolol during the evolution of an acute myocardial infarction increases the serum potassium concentration and reduces the incidence of hypokalaemia. The reduction in hypokalaemic episodes in the timolol group occurred despite there being more hypokalaemic patients in this group before treatment. The treatment groups were otherwise well balanced with respect to heart failure[10] and diuretic treatment.

Table 3 *Cumulative creatine kinase release (U/l) according to serum potassium concentrations in patients treated with placebo or timolol. Values are mean (SEM)*

	Serum potassium concentration (mmol/l)	
	≤3·5	*≥3·6*
Placebo	2068 (250) n=15	2344 (272) n=37
Timolol	1675 (728) n=7	1676 (125) n=47

A transient rise in mean serum potassium concentration occurred in both the placebo and timolol groups and reached a maximum four hours after treatment—that is, nearly eight hours after the estimated onset of infarction. The serum potassium concentration returned to pretreatment values in both treatment groups within 24 hours without any change in the regimen of the test drugs.

Treatment with diuretics before or during the first hours after admission abolished the rise in mean serum potassium concentration in the placebo but not in the timolol group (Fig. 1a). Treatment with diuretics alone reduced the mean serum potassium concentration but it still increased in patients treated with diuretics and timolol (Table 1). Diuretics increased and timolol reduced the number of patients with hypokalaemia (Table 2), indicating that timolol and diuretics have opposing effects on the serum potassium concentration.

The mechanism behind the initial rise in serum potassium concentration is unclear. At the onset of ischaemia there is a rapid loss of intracellular potassium in the myocardium, which causes a rise in coronary sinus potassium.[13 14] An average infarction of about 40 g of myocardium with about 0·1 mmol of potassium per gram could add about 4 mmol of potassium to the bloodstream. This mechanism may explain the transient rise in serum potassium concentration and the positive correlation between the ultimate infarct size and the change in serum potassium concentration.

The initial rise in serum potassium concentration is unlikely to have been caused by heart failure with poor peripheral circulation, as clinically overt heart failure did not occur in the patients shown in Fig. 1b. Nevertheless, certain mechanisms leading to increases in serum potassium concentration, as occur during exercise,[15] remain to be elucidated, and these may also contribute to the rise in serum potassium concentration seen during myocardial infarction in our study.

It has been clearly shown in normal volunteers that serum potasssium concentrations fall promptly in response to infusion of adrenaline.[8 16] If there was an outpouring of catecholamines in the immediate phase of evolving infarction then this would cause a fall in serum potassium concentration. This has been clinically described as an acute hypokalaemic syndrome and appears to occur in many acutely ill patients as well as in patients with acute infarction.[17] As the potassium concentrations in our study were not measured until almost four hours after the onset of symptoms it is quite likely that we missed the early and more pronounced falls in potassium concentration and that the early rise in potassium concentration in the placebo group was a recovery phenomenon from catecholamine induced hypokalaemia. The greater rise seen in the timolol group could be a combination of this recovery effect together with a specific drug effect on potassium movement.

Timolol may affect serum potassium concentration in several ways. A rise in serum potassium concentration is opposed by the adrenaline mediated peripheral uptake of potassium in skeletal muscle.[18] This beta$_2$ receptor effect of adrenaline is blocked by timolol.[8] A rise in potassium concentration in the timolol group may also partly have resulted from unopposed alpha effects of adrenaline.[7] A loss of intracellular potassium is readily reversible after the reversal of ischaemia.[13] A reversal of ischaemia caused by timolol, as occurred according to the accelerated reduction in the electrocardiographic ST segment elevations[10] and the 36% reduction in cumulative creatine kinase release, would be expected to reduce the rise in serum potassium concentration. Thus several mechanisms could have caused the weaker correlation between cumulative creatine kinase release and the change in serum potassium concentration in the timolol group compared with the placebo group. Concentrations of renin, aldosterone, and insulin were not measured in this study, but others have shown the effect of beta$_2$ blockade on serum potassium to be independent of these hormones.[16 18] Urinary potassium output was not measured, but a negative potassium balance has previously been found during beta blocker treatment.[9]

The clinical implications of the alterations in serum potassium concentration during evolving myocardial infarction and the effect of timolol on these alterations are not clear, and electrophysiological studies in nonischaemic hearts suggest that hypokalaemia may cause cardiac arrhythmias.[4 19] An inverse relation between serum potassium concentration $<5{\cdot}2$ mmol/l and the occurrence of ventricular fibrillation in acute myocardial infarction has been reported.[3] This does not, however, imply a definite causal relation. On the other hand, if the relation is causal then even the moderate differences in serum potassium concentration between the treatment groups in this study may be of importance.[3]

Hyperkalaemia is not associated with an increased likelihood of ventricular arrhythmias at concentrations seen during acute myocardial infarction.[1–3 17] In this study, hyperkalaemia occurred mostly at serum potassium concentrations of $<6{\cdot}0$ mmol/l and is therefore not a problem in patients selected for treatment with beta blockers during acute myocardial infarction. More severe hyperkalaemia may, however, be expected in patients with acidosis and renal failure.

Hypokalaemia was not related to infarct size, and the timolol treated patients with a serum potassium concentration $\geqslant 3{\cdot}6$ mmol/l did not have significantly larger infarctions than the hypokalaemic patients in the same treatment group (Table 3). The protective effect of timolol on hypokalaemia was therefore not restricted to those with large infarctions.

Although higher circulating catecholamine concentrations are seen in large[6] rather than small infarctions, thus tending to decrease serum potassium concentrations,[5] hypokalaemia is opposed by a rise in serum potassium concentration probably caused by the release of potassium from the ischaemic myocardium. In patients not treated with diuretics the net result, however, is a larger initial increase in serum potassium concentration in the large compared with the small infarctions. Blocking the adrenaline induced peripheral uptake of serum potassium concentration with timolol did not lead to significantly higher serum potassium concentrations compared with placebo, but the comparison is confounded by the significantly smaller infarct size in the timolol group. Patients with the large infarctions are more likely to receive intravenous diuretic treatment, which may initially abolish the rise and subsequently decrease serum potassium concentrations, as was seen in the placebo group. Thus a balance exists between the forces increasing and decreasing serum potassium concentrations, which as a result, when the balance is disturbed, does not confine hypokalaemia to any particular infarct size at least during the early stages of myocardial infarction.

In summary, a moderate and transient rise in serum potassium concentration, which is quantitatively related to infarct size, is seen during the evolution of acute myocardial infarction. The rise is counteracted both by treatment with diuretics, which also cause episodes of hypokalaemia, and by a tendency for hypokalaemia, which is probably caused by sympathetic stimulation. Timolol causes a rise in serum potassium concentration irrespective of diuretic treatment and prevents hypokalaemia. This effect may have important clinical implications for myocardial ischaemia, arrhythmias, and sudden death.

This study was carried out on behalf of the International Collaborative Study Group.

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Cellular immunity in congestive cardiomyopathy
The normal cellular immune response

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SUMMARY In vivo and in vitro tests of cellular immunity were studied in patients with congestive cardiomyopathy to determine whether these patients have normal or depressed cell mediated immunity to common environmental antigens and mitogens. No abnormality was found, but this does not exclude the possibility that transient depression of cell mediated mechanisms occurs early in the illness before clinical presentation.

Congestive cardiomyopathy is, by definition, of unknown aetiology[1] and may represent a group of diseases with a common end stage.[2] The role of viral infection of the heart progressing to cardiomyopathy has received considerable attention,[3 4] and a link with an immunological abnormality has been proposed.[5 6] Animal studies suggest that alterations in the immune status at the time of viral infection may influence the type and extent of damage to the myocardium in the short and long term.[7–9] Alternatively, once a virus has initiated damage abnormal immunological mechanisms may then perpetuate the damage.[10] Remembering that there may be several different aetiologies in congestive cardiomyopathy, it is also possible that those patients who go on to develop heart disease may have a primary immunological abnormality in contrast to those who recover completely from an acute insult.

The search for a humoral abnormality has not yielded consistent or convincing evidence of antibody mediated damage to the myocardium.[11 12] Various abnormalities of cellular immunity have been reported in congestive cardiomyopathy including an abnormal cellular immune status,[13 14] hypersensitivity and cytotoxicity to cardiac antigen preparations,[14–16] and abnormal suppressor T cell function.[17 18] This study examines the ability of patients with congestive cardiomyopathy to mount a normal cellular immune response compared with normal individuals and patients with ischaemic heart disease. Suppressor and helper T cell numbers were also measured (function was not tested) to see if there was a quantitative abnormality of these cells in cardiomyopathy.

Patients and methods

Three groups of patients were studied (Table 1). The congestive cardiomyopathic group consisted of 27 patients diagnosed according to the classification of Goodwin and Oakley[1]: all but two underwent cardiac catheterisation confirming normal coronary arteries and a left ventricular endomyocardial biopsy, the results of which were consistent with congestive cardiomyopathy.[19] The two exceptions had the diagnosis confirmed at necropsy. Twenty eight patients with ischaemic heart disease were matched with the cardiomyopathic group for symptoms using the New York Heart Association classification (Table 1) at the time of first venesection. Eighteen normal healthy controls, age and sex matched with the congestive cardiomyopathic group, comprised the third group.

The general status of patients' cellular immunity was assessed by in vivo skin testing to common antigens, in vitro leucocyte migration inhibition to common environmental antigens, and in vitro lymphocyte transformation to non-specific mitogens. Suppressor and helper T cells were counted in eight subjects from each of the three groups using mouse monoclonal antibodies produced against T cells.

The reagents used were: tuberculin PPD (Evans Medical Limited); streptokinase/streptodornase (Lederle Laboratories); *Candida albicans* (Bencard); physiological saline; BCG vaccine (Evans Medical Limited); preservative free heparin sodium (1000

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Table 1 *Details of patient groups*

Group	*No of patients*	*Sex (M/F)*	*Age (yr) (mean (SD))*	*NYHA class*				
				I	*IIa*	*IIb*	*III*	*IV*
Congestive cardiomyopathy	27	23/4	50 (11)	1	7	7	6	6
Ischaemic heart disease	28	23/5	56 (8)	3	6	6	10	3
Normal	18	15/3	46 (12)					

NYHA, New York Heart Association classification.

units/ml) (Duncan, Flockhart and Co Ltd); RPMI medium 1640 (Gibco Biocult) supplemented with 100 units/ml penicillin and 100 μg/ml streptomycin; fetal calf serum (Gibco); AB serum (Blood Transfusion Service); dextran 110 in physiological sodium chloride (Fisons); Ficoll-Triosil (Pharmacia, Nyegaard)[20]; tritiated thymidine (Amersham)[20]; scintillation fluid[20]; monoclonal antibody OKT3, OKT4, OKT8 (Orthoclone); fluorescein conjugated antimouse IgG (Meloy); and glycerol with paraphenylenediamine (PPD).

Intradermal skin tests were performed using 5 units tuberculin PPD, 10/2·5 units streptokinase/streptodornase, and 100 units *Candida albicans*. Each vial of streptokinase/streptodornase was reconstituted in saline, dialysed in saline for 48 hours to remove the preservative thiomersal, and further diluted to 100 units/ml streptokinase with saline. The skin tests were performed after the in vivo studies were complete and the response of the skin tests measured and graded at 48 hours: grade 1 represented erythema $\geqslant$10 mm without induration or with induration up to 5 mm; grade 2, induration between 6 and 10 mm; grade 3, induration between 11 and 20 mm; grade 4, induration >20 mm.[21]

LEUCOCYTE MIGRATION INHIBITION

The antigens used were BCG vaccine and streptokinase/streptodornase. The optimal antigen concentrations were determined before the study to avoid antigen toxicity, which hinders cell migration. A viability count was used to assess cytotoxicity to human leucocytes; >15% cell death and clumping of cells was taken to represent cytotoxicity. A dose-response curve was constructed and antigen concentrations below the cytotoxic range were used in the studies. For each test, a BCG pellet was suspended in 1 ml water for injection and varying concentrations made using tissue culture medium (RPMI with 10% fetal calf serum). The streptokinase/streptodornase was prepared as for the skin test and three different concentrations made at the time of the test using a tissue culture medium. A fresh sample of venous blood (16–20 ml) was collected from each patient in a sterile container with 0·4 ml heparin. Leucocytes were separated by adding 10 ml dextran and incubating at 37°C for 30 minutes. The leucocyte rich layer was removed and centrifuged at 400 *g* for 10 minutes at room temperature. The supernatant was discarded and the cells resuspended and washed in medium three times. The cells were then counted and resuspended at a dilution of 30×10^6 cells/ml. The cells were packed in capillary tubes (20 μl Volupette Pipets, Dade), plugged at one end with hard wax, and centrifuged at 300 *g* for 10 minutes. The antigens were put into the wells of a leucocyte migration plate (Sterilin) in a random manner, three wells for each antigen concentration and three wells containing tissue culture medium alone to act as a control. The capillary tubes were scored at the cell-fluid interface and two capillaries placed in each well secured by a plug of soft wax; the wells were covered with a coverslip, and an airtight seal ensured by using soft wax on the rim of the wells. Each plate was incubated for 18 hours at 37°C. The plates were then projected and the areas of migrating cells drawn on to paper; the areas were measured using a planimeter and the mean value of each antigen dilution divided by the mean control value (migration index). The coefficient of variation for the control wells had to be <10%. A migration index <0·80 represented inhibition for both BCG[22] and streptokinase/streptodornase.[23]

LYMPHOCYTE TRANSFORMATION

Phytohaemagglutinin and pokeweed mitogen were the mitogens used. Fresh venous blood was obtained from each patient in a sterile container with 0·4 ml heparin. The blood was layered on to Ficoll-Triosil and centrifuged at 400 *g* for 30 mins. The lymphocytes were removed from the serum-Ficoll-Triosil interface and washed in RPMI at 400 *g* for 10 minutes. Washing was repeated three times. The lymphocytes were counted and diluted to a concentration of 1×10^6 cells/ml in medium (10% AB serum in RPMI). Then a 0·1 ml cell suspension was placed in each well of a microtitre plate (Sterilin). A range of concentrations for both antigens was prepared using RPMI and each concentration added to three wells; each plate had triplicate control wells containing no antigen. The plates were incubated at 37°C in a humidified gassed incubator for 72 hours for phytohaemagglutinin and for seven days for pokeweed mitogen. Twenty four hours before the end of incubation, 0·5 μCi (0·02 MBq) tritiated thymidine was added to each well. After incubation, the cultures were harvested using a multiple cell culture harvester (Skatron, Flow). The dried harvester filters were placed in vials with 2 ml scintillation fluid and the degree of incorporation of label into cellular DNA measured using a scintillation counter. The results were expressed as the ratio of disintegrations per minute for each antigen dose to the unstimulated control value after correction for quenching and background subtraction.[20]

SUPPRESSOR AND HELPER T CELL MEASUREMENTS

Lymphocytes were prepared as for lymphocyte transformation. After counting, the lymphocytes were diluted to a concentration of 5×10^6 lymphocytes/ml with RPMI medium. Two hundred microlitres (1×10^6 cells) were put into four glass tubes and the monoclonal antibodies added: 5 μl of monoclonal antibody to helper cells (OKT4), to suppressor cells (OKT8), and to all mature peripheral blood T lymphocytes (OKT3) were each added to one glass tube, and the fourth had no monoclonal antibody in order to act as a control. The tubes were kept in an ice bath and mixing allowed to take place for at least one hour at 4°C. The cells were washed three times with 5% fetal calf serum in RPMI medium for 10 minutes at 700 *g* at 4°C. One drop (0·03 ml) fluorescein conjugated antimouse IgG was added to each test tube including the control and the cells allowed to stand for half an hour in an ice bath at 4°C. The cells were washed three times at 4°C with 5% fetal calf serum in medium as before and the supernatant discarded. The cells were resuspended gently, mounted in glycerol PPD, and viewed under the fluorescence microscope. Three fields containing 30–40 lymphocytes each were counted and the number showing fluorescence expressed as a percentage of the total lymphocytes counted.

MICROSCOPY

A Leitz Ortholux II microscope with Epi illumination using a super pressure mercury lamp source (HBO 50), a Balzer filter exciter, a red cutoff filter (RG8), and a yellow barrier filter (Kodak Wratten) was used.

STATISTICAL ANALYSIS

Comparisons between groups for tuberculin and streptokinase-streptodornase skin tests were made using the χ^2 test for independent samples or the Fisher exact probability test where sample numbers were small.[24] The Kruskal-Wallis one way analysis of variance was used to test statistical significance of transformation and migration inhibition results.[24]

Results

Table 2 shows the results of the skin tests. There were no significant differences in the number of positive responders between the groups using tuberculin ($0·5 > p > 0·3$), streptokinase ($0·7 > p > 0·5$), or candida. Using tuberculin, 58% of the congestive cardiomyopathy group and 57% of the normal group had a grade 2 or higher positive skin test compared with only 25% of the ischaemic heart disease group; similarly, 44% of congestive cardiomyopathic patients and 46% of the normal group had at least a grade 2 response with streptokinase compared with only 19% in the ischaemic group. Four patients in the cardiomyopathy group and six in the ischaemic heart disease group did not give a response with any antigen; this was significant for the ischaemic heart disease group when compared with the normal controls ($p = 0·01$) but not for the congestive cardiomyopathy group.

Figure 1 shows the leucocyte migration inhibition results at the highest concentration of each antigen. Seventeen of 27 cardiomyopathy patients, 20 of 27 ischaemic patients, and 11 of 18 normal controls were inhibited by BCG antigen at its highest concentration. Similarly, eight, nine, and six of the cardiomyopathic, ischaemic, and normal groups respectively were inhibited with streptokinase/streptodornase antigen.

Table 2 *Skin test results. Figures are numbers of patients*

Antigen and patient group	*Grade of response*					
	Negative	*1*	*2*	*3*	*4*	*Total No*
Tuberculin PPD:						
Congestive cardiomyopathy	7	1	1	7	3	19
Ischaemic heart disease	8	4	1	2	1	16
Normal	4	2	3	1	4	14
Streptokinase/streptodornase:						
Congestive cardiomyopathy	8	2	3	3	2	18
Ischaemic heart disease	8	5	2	1	0	16
Normal	4	3	1	5	0	13
Candida albicans:						
Congestive cardiomyopathy	16	0	1	0	1	18
Ischaemic heart disease	14	1	1	0	0	16
Normal	11	1	2	0	0	14

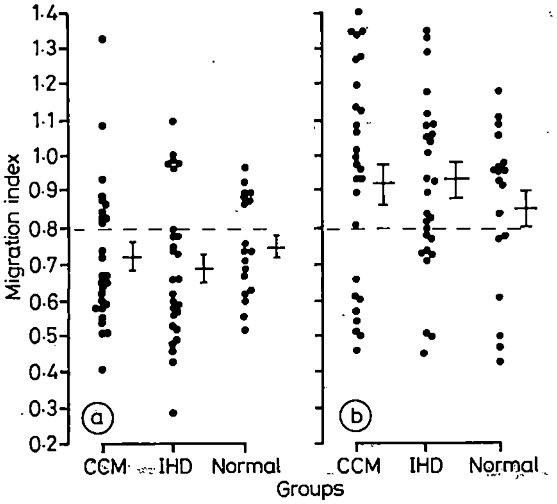

Fig. 1 *Migration index using (a) BCG antigen (30 µg/ml) and (b) streptokinase (SK)/streptodornase (3000 u/ml SK) for each subject in the three groups. Values <0·8 represent inhibition. The mean value and standard error for each group is indicated. CCM, congestive cardiomyopathy; IHD, ischaemic heart disease.*

Lower antigen concentrations showed less inhibition in all groups, the mean migration indices tending to approach 1·00.

Figure 2 shows the lymphocyte transformation results for the three highest concentrations for each antigen. All patients and normal controls showed stimulation with the mitogens, although the range of response was very wide in each group. None of the differences between the groups was statistically significant.

Table 3 *Mean (SD) percentage of helper and suppressor T cells*

Patient group	*Helper*	*Suppressor*	*Total*
Congestive cardiomyopathy	45 (8)	18 (8)	52 (10)
Ischaemic heart disease	43 (9)	15 (8)	57 (14)
Normal	40 (9)	23 (5)	58 (11)

Table 3 shows the mean percentage value and standard deviation for the helper, suppressor, and total mature T lymphocytes in each group. The percentage of control staining was <2%. There were no group differences.

Discussion

Leucocyte migration inhibition, delayed hypersensitivity skin tests, and lymphocyte transformation are primarily tests of cell mediated immune responses and involve the release of soluble factors—lymphokines—which are not antibodies.[25] Lymphokines are released from lymphocytes previously sensitised to the antigen under examination in the migration inhibition and skin tests.[26 27] BCG, tuberculin PPD, *Candida albicans,* and streptokinase represent common environmental antigens to which many people have had previous exposure, and therefore leucocyte migration inhibition and positive skin

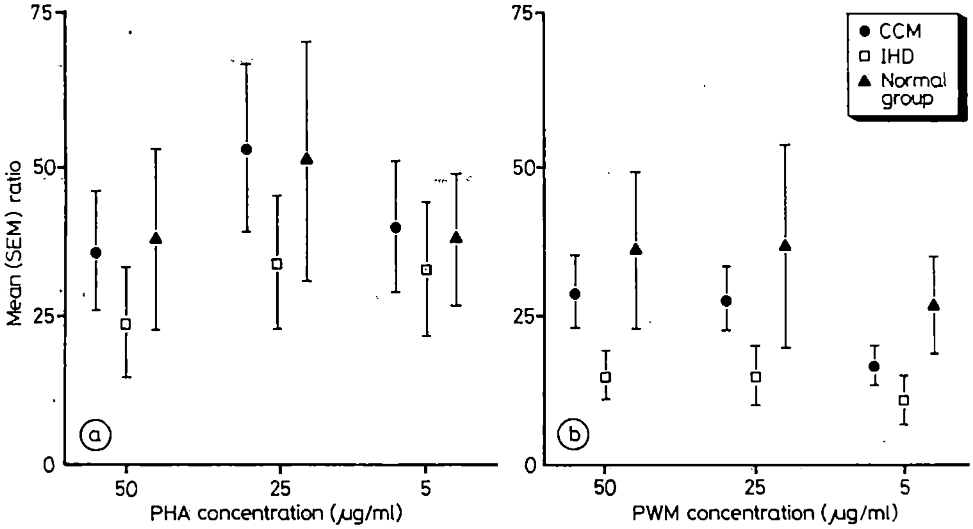

Fig. 2 *Lymphocyte transformation to (a) phytohaemagglutinin (PHA) and (b) pokeweed mitogen (PWM) expressed as the mean ratio of disintegrations per minute for each antigen concentration to the unstimulated control for each patient group. CCM, congestive cardiomyopathy; IHD, ischaemic heart disease; SEM, standard error of the mean.*

tests would be expected to occur in a proportion of a normal population.[25,28,29]

Both T and B lymphocytes can be stimulated by antigen to form blast cells and synthesise DNA; the incorporation of tritiated thymidine during this process allows the blastogenic activity to be measured.[30] Phytohaemagglutinin and pokeweed mitogen are non-specific stimulants of lymphocytes not requiring presensitisation[31,32] and stimulate T cells mainly, B cells predominantly only secondarily.[21,33]

These tests are useful in determining whether cellular immunity is normal or depressed, but they are testing only a small part of a complex system.[27]

In our study patients with congestive cardiomyopathy did not differ in any way from the normal control group when tested by leucocyte migration, lymphocyte transformation, or skin testing; this contrasts with other studies. Das *et al* claimed that over 40% of patients with congestive cardiomyopathy had abnormal cell mediated immunity.[13] In fact, their results for leucocyte migration inhibition showed no significant mean group difference, but 42% of patients with cardiomyopathy lay outside the 90% confidence limits of the control group. Lymphocyte transformation results were not significantly different from those of a miscellaneous heart group, but both were significantly different from the normal control group, suggesting that the abnormality was not specific to cardiomyopathy. No other studies have undertaken a comprehensive survey of cell mediated immunity[34]; the results of Das *et al*[13,14] suggest that only single indices of cell mediated immunity were tested in each group, and there were no observations that abnormal lymphocyte transformation results, for instance, coincided with the same population of congestive cardiomyopathy patients showing abnormal leucocyte migration inhibition.

The ischaemic heart disease group had similar migration and transformation results but responded poorly to skin testing when compared with both the cardiomyopathic and normal groups. A positive skin test in this study was defined according to Bates *et al*,[21] but not everyone would accept erythema alone, or induration <5 mm, as positive.[35] In this case, the discrepancy between the ischaemic group and the cardiomyopathy and normal groups is emphasised. Depressed cellular responsiveness can occur with increasing age, after viral illness or general anaesthesia, and where there is severe debilitating disease; leucocytosis, fever, anaemia, and weight loss are also strongly interrelated.[36] Few of these factors apply to ischaemic heart disease and those which might also apply to congestive cardiomyopathy (except for the higher mean age of the ischaemic group). It was not possible to differentiate the groups by severity of symptoms or number of deaths (seven in the cardiomyopathy group, six in the ischaemic heart disease group) during the study. No quantitative abnormality of suppressor or helper T cells was found, but function was not assessed.

Patients with congestive cardiomyopathy appear to have normal cellular immunity by the time they are diagnosed. This does not exclude the possibility that cellular immunity may be depressed transiently at the time of the initiation of the disease, for example after a viral illness, but it does suggest that patients with congestive cardiomyopathy have the potential to mount a type IV hypersensitivity response which may be important in the pathogenesis of the disease.

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Cellular immunity in congestive cardiomyopathy

Hypersensitivity to cardiac antigens

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SUMMARY The presence of type IV hypersensitivity to cardiac antigens in 26 patients with congestive cardiomyopathy was sought by two in vitro techniques. Neither test showed a significant group abnormality, but 10 patients did have hypersensitivity to heart antigen, in particular to congestive cardiomyopathic heart antigen. These patients were characterised by worse haemodynamic data and a more rapid and malignant course of the disease than in the rest of the group.

Immunological abnormalities are known to occur in congestive cardiomyopathy, but their role and importance in aetiology have not been determined.[1 2] The possibility that an insult to the heart such as a viral infection might initiate damage which immunological mechanisms then perpetuate has been suggested.[3 4] Raised virus titres have been reported in congestive cardiomyopathy without the isolation of virus particles in the myocardium.[4 5] Animal experiments have shown that acute viral infections of the heart can progress to chronic myocardial damage where evidence of virus is absent after the first few days of infection[6]; T cell function appears to be important in determining the long term outcome of these infections.[7 8] A viral antigen or an abnormal cardiac antigen exposed by a virus may be responsible for setting up a hypersensitivity reaction which would continue after the infection had disappeared. Type IV hypersensitivity to heart antigens has been reported in a proportion of patients with congestive cardiomyopathy,[9 10] but whether the abnormality is primary or secondary, or whether those with such apparent autoimmunity comprise only a subset of patients with congestive cardiomyopathy, or whether the tests used to detect hypersensitivity are not sensitive enough is not known.

This study examined the possibility that type IV hypersensitivity to cardiac antigens is an underlying mechanism of damage in congestive cardiomyopathy. In vitro hypersensitivity to antigen preparations made from a normal heart, two different congestive cardiomyopathic hearts, and a hypertrophic cardiomyopathic heart was assessed in two groups of patients with congestive cardiomyopathy or ischaemic heart disease and in normal healthy controls.

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Patients and methods

Twenty six patients with congestive cardiomyopathy diagnosed according to the classification of Goodwin and Oakley[11] were studied. All but two patients had undergone cardiac catheterisation, which showed normal coronary arteries and histological compatibility with the diagnosis on endomyocardial biopsy[12]; in the two exceptions, the diagnosis was confirmed at necropsy. For comparison, a group of 26 patients with ischaemic heart disease matched for symptoms using the New York Heart Association classification were studied (Table 1); mean haemodynamic data are also shown in Table 1 for the two patient groups, and there were no significant differences between them (Student's unpaired t test). A third group of 18 normal healthy controls were age and sex matched with the cardiomyopathy group.

Type IV hypersensitivity is a cell mediated (or delayed) type of hypersensitivity usually involving T lymphocytes and non-specific inflammatory cells. It was studied by two in vitro techniques: leucocyte migration inhibition and lymphocyte transformation using cardiac muscle preparations as the antigens. Details of the methods are previously described by Lowry *et al*,[13] and the procedures in this study were identical except for the use of different antigens.

'able 1 *Details of patients*

atient group	*No of patients*	*Mean (SD) age (yr)*	*Sex*	*NYHA class*					*Cardiac catheterisation data*			
			(M/F)	*I*	*IIa*	*IIb*	*III*	*IV*	*No of patients*	*Mean (SD) LVEDP (mm Hg)*	*Mean (SD) LVESI (ml/m²)*	*Ejection fraction (%)*
ongestive cardiomyopathy	26	50 (11)	22/4	1	7	6	6	6	24	17 (8)	147 (88)	34 (21)
:chaemic heart disease	26	55 (8)	22/4	3	6	4	10	3	22	26 (10)	126 (61)	28 (23)
'ormal	18	46 (12)	15/3									

YHA, New York Heart Association; LVEDP, left ventricular end diastolic pressure; LVESI, left ventricular end systolic index.

ANTIGEN PREPARATION

Four different human hearts were used to prepare the antigens: (*a*) a normal heart obtained within 14 hours of death from a woman who died after trauma; (*b*) a congestive cardiomyopathic heart (A) confirmed by cardiac catheterisation and biopsy and later at necropsy from a 16 year old boy with a rapidly progressive illness (two months) and no history of preceding viral illness; (*c*) a congestive cardiomyopathic heart (B) obtained at cardiac transplantation from a 42 year old man with a 15 year history of heart failure which began after a flu-like illness in 1966; and (*d*) a hypertrophic cardiomyopathic heart from an 18 year old man in whom the diagnosis was made by echocardiography two days before death and confirmed at necropsy (one of the patient's siblings and an uncle had died of hypertrophic cardiomyopathy). The hearts were stored at −70°C before antigen preparation.

A saline soluble extract of each heart was prepared in an identical manner. A piece of ventricle (approximately 100 g wet weight) was thawed and finely sliced and then homogenised in sterile physiological saline for 15 minutes. The mixture was centrifuged at 1600 g for 10 minutes and the supernatant retained. This was filtered through an 8·0 μm, a 0·45 μm, and finally through a 0·22 μm filter in a sterile 200 ml Millipore membrane filtration unit. Sterility was confirmed by standard culture procedures. Protein concentration of each preparation was measured using a modification of the technique described by Daughaday *et al.*[14] The antigen preparations were stored in aliquots at −70°C until used. A dose-response curve was plotted for each antigen to determine the optimum range of antigen concentration that would detect sensitised cells without causing cytotoxicity. Cytotoxicity was assessed using a viability count: >15% cell death and clumping of cells was taken to represent cytotoxicity.

STATISTICAL ANALYSIS

The Kruskal/Wallis one way analysis of variance was used to test the significance of difference between the three groups for leucocyte migration inhibition and lymphocyte transformation.[15] The χ^2 test (or the Fisher exact probability test where numbers were small) was used as a test of significance when inhibited and non-inhibited groups were compared.[15] The Mantel-Haenszel test was used to test the significance of differences between the groups for survival.[16]

Results

The leucocyte migration inhibition test did not show significant differences between the three groups when tested with normal heart antigen ($0{\cdot}99>p>0{\cdot}98$), congestive cardiomyopathic (A) antigen ($0{\cdot}90>p>0{\cdot}80$), congestive cardiomyopathic (B) antigen ($0{\cdot}30>p>0{\cdot}20$), or hypertrophic cardiomyopathic antigen ($0{\cdot}50>p>0{\cdot}30$). A migration inhibition index $<0{\cdot}80$ is usually considered to represent inhibition.[17] Table 2 shows the percentage of patients showing such inhibition for each group and each antigen. Although more of the congestive cardiomyopathic group were inhibited by the normal and congestive cardiomyopathic (A) and (B) heart antigens, none of these differences reached statistical significance.

Not all the patients were tested successfully with all antigens as some died or had operations before testing was complete. The patients were initially tested with normal and congestive cardiomyopathic (A) hearts so the number of results are greater with these antigens. Using these antigens, 10 of 25 congestive cardiomyopathic patients, four of 22 ischaemic heart disease patients, and two of 18 normal controls were

Table 2 *Percentage of patients inhibited with heart antigens*

Patient group	*Antigen*			
	Normal heart	*CCM (A)*	*CCM (B)*	*HCM*
Congestive cardiomyopathy	27	28	37	16
Ischaemic heart disease	8	9	13	24
Normal	11	6	21	29

CCM (A) and CCM (B), from two different patients with congestive cardiomyopathy; HCM, hypertrophic cardiomyopathy.

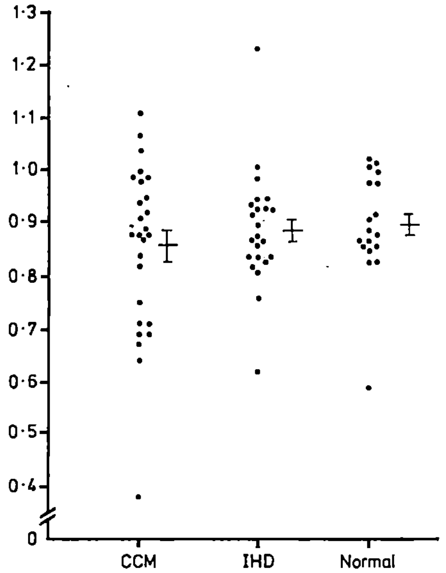

Fig. 1 *Individual migration index to congestive cardiomyopathic (A) antigen in patients with congestive cardiomyopathy (CCM) or ischaemic heart disease (IHD) and normal subjects. Mean (SEM) values are shown.*

inhibited by one or both antigens (Fig. 1). There seemed to be a cluster of congestive cardiomyopathic patients showing inhibition compared with the other groups, but this did not reach statistical significance. Table 3 compares the mean age, haemodynamic data, and duration of symptoms of the 10 cardiomyopathic patients showing inihibition with normal heart and congestive cardiomyopathic (A) antigens with those of the rest of the group. There was a tendency for the patients showing inhibition to have worse haemodynamic data. Figure 2 shows the difference in survival between the 10 congestive cardiomyopathic patients who showed inhibition and the rest of the group. The difference in survival between the inhibited and non-inhibited cardiomyopathic groups was not significant (p>0·1), but the patient numbers were small.

Seven congestive cardiomyopathic patients were inhibited with congestive cardiomyopathic (A) antigen, and they also tended to have worse haemodynamic data than the rest of the group (Table 3). The mean duration of illness in these seven patients was 27 months compared with 48 months for the remainder of the group. Five of the seven died before the end of the study. The duration of illness for these five was 19 months, and all had been tested with congestive cardiomyopathic (A) antigen within three months of death.

One of the two normal controls who showed inhibition with normal heart antigen was the identical twin brother of one of the congestive cardiomyopathic patients who showed inhibition with both normal heart and congestive cardiomyopathic (A) antigens and who died. One normal control was inhibited with both normal and congestive cardiomyopathic (A) heart antigens. None of the ischaemic heart disease patients were inhibited with more than one antigen.

Testing with congestive cardiomyopathic (B) antigen did inhibit some different patients in the cardiomyopathic group, but there was some overlap with those already showing inhibition with other heart antigens. Finally, testing with hypertrophic cardiomyopathic antigen did not show inhibition predominantly in any one group, and there was overlap with patients showing inhibition with other antigens.

Figure 3 shows the lymphocyte transformation results; two different concentrations of normal heart antigen and congestive cardiomyopathic (A) antigen are represented. The variation in results was wide, but no stimulation occurred with either antigen, and there were no significant differences between the groups. In view of these results, lymphocyte transformation was not attempted with congestive cardiomyopathic (B) or hypertrophic cardiomyopathic antigens.

Table 3 *Comparison of data between inhibited and non-inhibited groups*

Patient group	*Mean (SD) Age (yr)*	*Mean (SD) LVEDP (mm Hg)*	*Mean (SD) LEVSI (ml/m²)*	*Mean (SD) ejection fraction (%)*	*Mean (SD) duration of symptoms (mth)*	*NYHA class*				
						I	*IIa*	*IIb*	*III*	*IV*
Congestive cardiomyopathy:										
Inhibited with normal heart or CCM (A) antigens or both	50 (14)	20 (6)	189 (93)	29 (21)	37 (29)	—	4	—	3	3
Inhibited with CCM (A) antigen only	48 (16)	20 (7)	190 (116)	35 (24)	27 (23)	—	3	—	2	2
Not inhibited with either normal heart or CCM (A) antigens	51 (8)	16 (9)	127 (81)	36 (21)	46 (52)	1	3	6	3	2
Ischaemic heart disease:										
Inhibited with normal heart or CCM (A) antigens	55 (7)	17 (10)	89 (115)	56 (43)		1	1	1	1	—

LVEDP, left ventricular end diastolic pressure; LVESI, left ventricular end systolic index; NYHA, New York Heart Association classification; CCM (congestive cardiomyopathic heart A antigen.

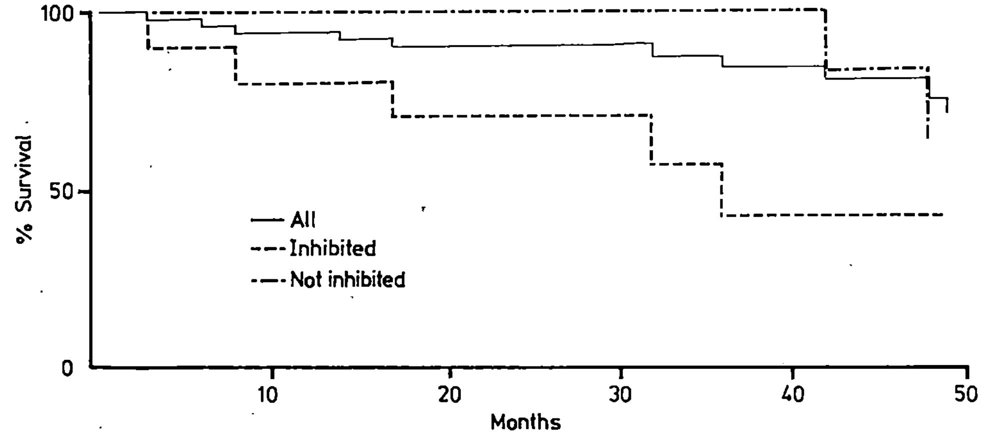

Fig. 2 *Survival curves for congestive cardiomyopathy patients seen during the past seven years (all), for the 10 patients inhibited with normal heart antigen or congestive cardiomyopathic (A) antigen, or both, and for the rest of the group not inhibited.*

Discussion

Lymphocyte transformation and leucocyte migration inhibition have been successfully used as tests of cellular hypersensitivity to various antigens.[18] Inhibition of leucocytes by lymphokines in the presence of tissue antigen suggests presensitisation of the cells, a response to heart tissue that would not be expected in a normal individual. Nevertheless, no test of cellular mechanisms proves that T cells are primarily responsible for tissue damage.[19]

Leucocyte migration inhibition has been widely used as a test of hypersensitivity and shown to correlate well with delayed type skin testing,[20] for example, in Mantoux positive and negative individuals.[21] In this study, no skin test was available, whereas in studies with other antigens in which skin testing was possible a migration index of 0·80 has separated the positive and negative responders[20 22] and has been applied in similar studies.[23]

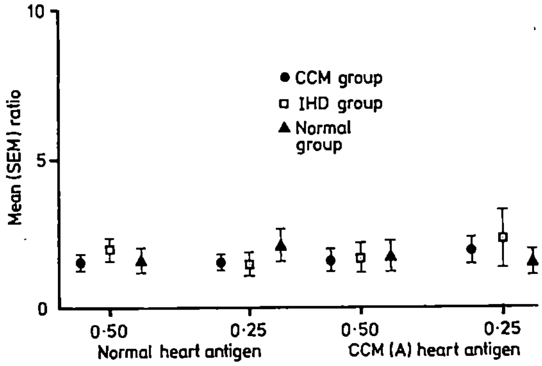

Fig 3 *Lymphocyte transformation results to normal heart antigen and congestive cardiomyopathic (A) (CCM (A)) antigen at two different antigen concentrations (mg/ml) expressed as the mean (SEM) ratio of test to control counts. CCM, congestive cardiomyopathy; IHD, ischaemic heart disease.*

In this study, neither leucocyte migration inhibition nor lymphocyte transformation to heart antigens showed significant differences between the groups. There did, however, appear to be a group of patients in the cardiomyopathic group who did show leucocyte migration inhibition (migration index <0·80) when compared with the other groups using a normal heart and congestive cardiomyopathic antigens; the numbers did not reach statistical significance but the finding did raise some interesting points. One of the difficulties of this study was that by the very nature of the illnesses, patients in the ischaemic and cardiomyopathic groups died before all testing was complete. The group of 10 congestive cardiomyopathy patients showing inhibition to normal heart antigen and congestive cardiomyopathic (A) antigen had a 50% mortality compared with 11% for the rest of the group. The haemodynamic data suggested that the cardiomyopathy patients showing inhibition had worse ventricular function than the rest of the group. The congestive cardiomyopathy patients inhibited with congestive cardiomyopathic (A) antigen had worse haemodynamic data, a shorter duration of illness, and higher mortality (71%) compared with the remainder of the group. These trends may indicate that patients with congestive cardiomyopathy showing leucocyte migration inhibition to cardiac antigens have a more malignant illness and poorer prognosis. It is not clear whether this is cardiac tissue specific since other tissue preparations were not evaluated in this study, which concentrated on showing an effect of cardiac antigen preparation in the first instance. The few patients with ischaemic heart disease who showed inhibition with normal heart or congestive cardiomyopathic (A) antigens were not necessarily those with poor left ventricular function (Table 3) suggesting that such sensitisation is not merely the result of end stage cardiac damage whatever the cause.

These results are similar to those of other groups who have also found small numbers of patients within the cardiomyopathy group showing hypersensitivity to heart antigens.[10 24] There are several possible explanations for these findings. Differing aetiologies may lead to different antigens being exposed; for example, a virus might predispose to the exposure of a particular antigen so that only those patients sensitised to that particular antigen would show hypersensitivity. It is interesting that the congestive cardiomyopathic (A) heart antigen was from a boy who had a rapidly progressive illness, as had those showing inhibition with his heart. Different congestive cardiomyopathy antigens did not, however, identify separate and distinct groups of patients, but overlap was seen. The nature of the antigens in such preparations of heart muscle was very important. They undoubtedly consist of a mixture of soluble cytoplasmic and membrane proteins. Sterility was achieved by ultrafiltration, and this excluded the bulk of possible antigenic material especially membrane bound antigens. The use of a soluble antigen preparation in any case is less likely to cause inhibition than a particulate antigen.[17] It is possible that the major part of the antigen of prime importance is lost altogether in the preparation. It may be that hypersensitivity occurs terminally, and this would explain why inhibition was often present within three months of death. Also the response to the heart preparation did not seem to be specific to the cardiomyopathy group or indeed to patients with heart disease since even the normal group had individuals showing a positive response. It was of interest that the twin brothers both showed inhibition with normal heart antigens; perhaps it is these people who, with the appropriate stimulus, will procede to develop congestive cardiomyopathy.

In order to probe these findings further the preparation of a purer and more appropriate antigen will be necessary using both biochemical and immunological methods.

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Progression of hypertrophic cardiomyopathy
A cross sectional echocardiographic study

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SUMMARY The progression of hypertrophy was studied in 39 patients with hypertrophic cardiomyopathy by echocardiography at follow up from January 1979 to September 1983 (mean follow up 42 months). Thirty two patients were treated medically and 11 had had a septal myotomy-myectomy. Progression of the hypertrophy was noted in four patients treated with propranolol. An additional region in the left ventricular long axis plane was affected in two, extending to the apical region in one and to the basal region in the other, and an additional segment in the left ventricular short axis plane in two extending from the septum into the free wall. The electrocardiograms of these four patients showed a significant increase in QRS voltages (Sokolow-Lyon index increase >10 mm) and of the Romhilt-Estes score (increase ≥3 points) in two, development of a left bundle branch block in one, and no change in one. Progression of hypertrophy was seen in none of the 11 patients treated with myotomy-myectomy.

Thus echocardiography accurately detects the progression of hypertrophy in patients with hypertrophic cardiomyopathy, which may be prevented by septal myotomy-myectomy.

With echocardiography the familial occurrence of hypertrophic cardiomyopathy,[1–3] its morphological[4–6] and functional aspects,[7–9] and the effects of medical[10–12] and surgical treatment can be studied.[13 14] Based on the patterns of distribution of the hypertrophy, classification into subtypes of hypertrophic cardiomyopathy has been proposed.[15 16] The progression of hypertrophy has been assessed in patients by electrocardiography,[17] but because of its low sensitivity and specificity in detecting hypertrophy in these patients[18] this method may not be useful for studying its progression. The aim of this study was to investigate by serial electrocardiography and cross sectional echocardiography whether or not progression of hypertrophy occurs in hypertrophic cardiomyopathy.

Patients and methods

STUDY GROUPS

Two groups of patients with hypertrophic cardiomyopathy were studied: 39 treated medically (25 men and 14 women, age range 16–70 (mean 44) years) and 11 treated with septal myotomy-myectomy (six men and five women, age range 17–65 (mean 46) years). They were selected from a group of 67 patients with hypertrophic cardiomyopathy because the quality of their cross sectional echocardiograms allowed the endocardial and epicardial borders of the left ventricular free wall and the endocardial boundaries of the interventricular septum to be identified.

The diagnosis was based on the history, typical clinical signs, and the established echocardiographic criteria for hypertrophic cardiomyopathy as proposed by Goodwin.[19] Haemodynamic and angiographic studies were carried out in 25 of the 39 medically treated patients. A resting or provoked (isoproterenol infusion) left ventricular outflow gradient or both was noted in 13 of the 25 patients (range 20–155 mm Hg). Cardiac catheterisation was not performed in the 11 patients treated surgically. Table 1 shows the clinical data of the two groups. The indications for septal myotomy-myectomy were severe symptoms despite medical treatment with pronounced obstruction to left ventricular outflow at rest (≥50 mm Hg). Echocardiographic follow up data were available from

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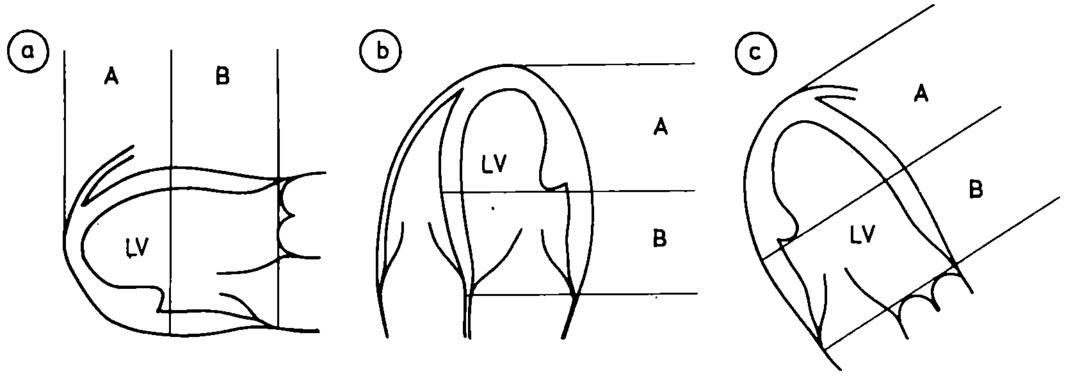

Fig. 1 *Diagram showing the principle of assessment of the regional distribution of the hypertrophy in hypertrophic cardiomyopathy from cross sectional echocardiograms in (a) the parasternal long axis view, (b) the apical four chamber view, and (c) the apical long axis view. The left ventricle (LV) is subdivided along its long axis into a basal region (B) and an apical region (A).*

Table 1 *Clinical data of the 50 patients with hypertrophic cardiomyopathy at the time of entry into the study. Figures are numbers of patients unless stated otherwise*

Clinical data	*Medically treated group (n=39)*	*Surgically treated group (n=11)*
Male/female	25/14	6/5
Mean age (yr)	44	46
NYHA class		
I	18	7
II	17	4
III	4	0
IV	0	0
Drug treatment:		
Propranolol (80–240 mg/day)	30	7
Verapamil (160–320 mg/day)	2	0

January 1979 to September 1983 (mean follow up 42 months). Each patient underwent at least three echocardiographic and electrocardiographic studies. No patient died during the follow up period.

ECHOCARDIOGRAPHY

Cross sectional echocardiograms were obtained using a phased array system (Toshiba SSH-10 with a 2·25 MHz transducer and Toshiba SSH-40A with a 3·5 MHz transducer). In each patient the parasternal long axis and short axis views at multiple levels and the apical four chamber and apical long axis views were obtained. Standard M mode echocardiograms of the left ventricle were obtained from selected long axis

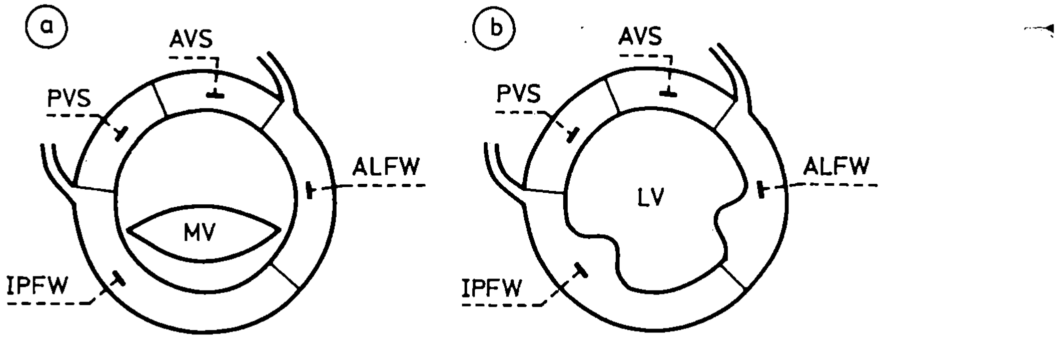

Fig. 2 *Diagram showing the cross sectional echocardiographic short axis views used for evaluating the segmental distribution of the hypertrophy in hypertrophic cardiomyopathy. The basal region (a) is at mitral valve level (MV) and the apical region (b) at papillary muscle level. The left ventricle (LV) is subdivided into four segments and insertion of the free walls of the right ventricle is used as a landmark to separate the interventricular septum from free wall. The interventricular septum is divided into anterior (AVS) and posterior (PVS) segments. The left ventricular wall is also divided into two segments, an anterolateral free wall (ALFW) which includes the anterolateral papillary muscle and an inferoposterior free wall (IPFW).*

Table 2 *Distribution of the hypertrophy by cross sectional echocardiography in the long and short axis of the left ventricle in 39 patients with hypertrophic cardiomyopathy. Figures are numbers of patients*

	Short axis				
Long axis	*Partial IVS*	*Entire IVS*	*IVS and partial FW*	*IVS and entire FW*	*Total (%)*
Basal region	1	1	1	0	3 (8)
Apical region	0	0	0	2	2 (5)
Basal and apical regions	2	13	8	11	34 (87)
Total (%)	3 (8)	14 (36)	9 (23)	13 (33)	

IVS, hypertrophy of the interventricular septum; FW, hypertrophy of the left ventricular free wall; partial IVS, hypertrophy of one septal segment (anterior or posterior); entire IVS, hypertrophy of both septal segments (anterior and posterior); partial FW, hypertrophy of one segment of the free wall (anterolateral or inferoposterior); entire FW, hypertrophy of both segments of the free wall (anterolateral and inferoposterior).

and short axis views for accurate wall thickness measurements.

Analysis of the echocardiograms

The videotaped cross sectional echocardiograms were carefully and independently reviewed in a random order by two observers who did not know the name of the patient or the date of examination. Hypertrophy was considered to be present if the thickness of the left ventricular wall was ≥15 mm. Using guidelines proposed by Maron and coworkers,[15] the segments of the left ventricular wall near to the lateral borders of the sector were considered hypertrophied when their thickness was ≥17 mm in order to avoid overestimation due to the limited lateral resolution.

The distribution of left ventricular hypertrophy was evaluated in both the long and short axis planes. In the long axis, the left ventricle was divided into two regions (Fig. 1): the basal region, from the cardiac base to a level just above the tips of the papillary muscles, and the apical region, from the papillary muscles to the cardiac apex. In the short axis plane (Fig. 2), at the level of the basal and apical region, the ventricular septum was divided in two segments, anterior and posterior. The left ventricular free wall was also divided into two segments at these levels, anterolateral and inferoposterior. A total of 1360 segments were analysed, and agreement between the observers in assessing the presence or absence of hypertrophy was obtained in 1331 (98%). For the remaining 19 segments, consensus was achieved with the help of a third observer.

The echocardiographic criteria used to detect progression of hypertrophy were (*a*) extension of the hypertrophy to another region, from the basal to the apical region and vice versa along the left ventricular long axis, and (*b*) extension of the hypertrophy to one or more segments of the same region along the left ventricular short axis.

ELECTROCARDIOGRAPHY

Standard 12 lead electrocardiograms were performed in all patients on the same day as the echocardiographic examination. Tracings were recorded with the patients in the supine position during quiet respiration. Amplitude measurements were obtained from five consecutive complexes to reduce variation by respiration. The presence of left ventricular hypertrophy was diagnosed using the point score system proposed by Romhilt and Estes[20] (≥5 points) and the Sokolow-Lyon index (SV1+RV5 >35 mm).[21] The electrocardiograms were analysed independently in random order by two observers who did not know the name of the patient or the date of examination.

Results

MEDICALLY TREATED GROUP

Table 2 shows the distribution of hypertrophy seen by cross sectional echocardiography in the 39 medically treated patients. Serial cross sectional echocardiographic studies showed progression of hypertrophy in four patients. In two patients it affected an additional region in the left ventricular long axis plane. In the first patient the initial septal hypertrophy in the basal region extended into the apical region and in the second it extended from the apical to the basal region. The extension of the hypertrophy into the basal region was also evident on M mode echocardiography (Fig. 3a and 3b). In two other patients progression of the hypertrophy affected another segment of the same region along the left ventricular short axis, the inferoposterior segment of the free wall in one patient (Fig. 4) and the anterolateral segment of the free wall in the other (Fig. 5). Progression of the hypertrophy was seen after two years of follow up and was confirmed in subsequent studies. Table 3 shows the clinical characteristics of the four patients.

The electrocardiograms showed an increase in the indices of left ventricular hypertrophy in two of these patients (Fig. 6). A third patient developed left bundle branch block, and no electrocardiographic changes were noted in the fourth.

The mean age and duration of follow up of these four patients did not differ from those without echocardiographic evidence of progression of hyper-

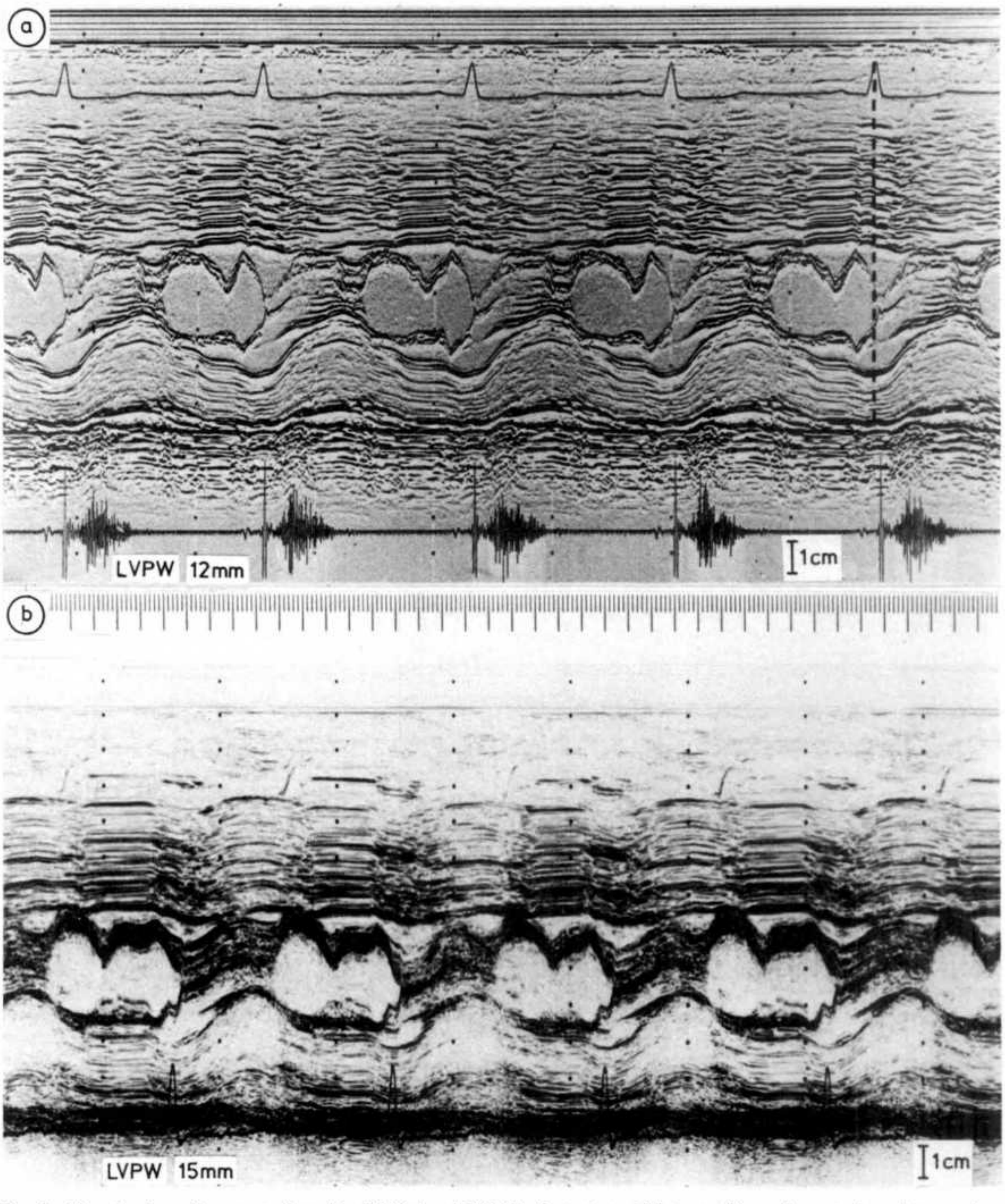

Fig. 3 *M mode echocardiograms performed in 1979 (a) and 1982 (b) of a patient with hypertrophic cardiomyopathy and progression of hypertrophy present along the long axis from the apical to the basal regions of the inferoposterior wall. (a) The interventricular septum at the level of the basal region appeared to be considerably hypertrophied. The left ventricular posterior wall (LVPW) had a thickness of 12 mm. (b) After three years the thickness of the left ventricular posterior wall had increased to 15 mm.*

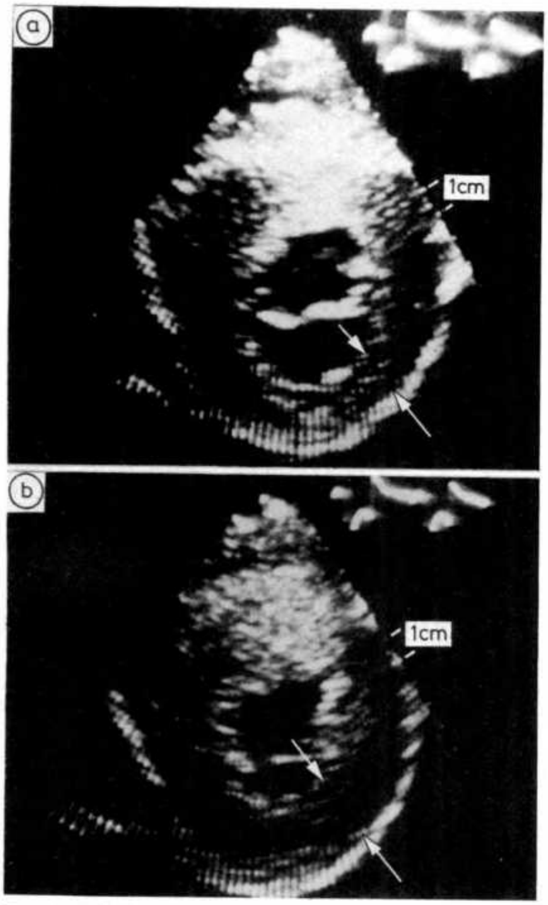

Fig. 4 *End diastolic cross sectional echocardiographic parasternal short axis views at the level of the basal region of a patient with hypertrophic cardiomyopathy, showing (a) hypertrophy of the entire septum and of the anterolateral segment of the free wall but normal thickness of the inferoposterior segment of the free wall and (b) hypertrophy in the inferoposterior segment of the free wall (arrows) three years later.*

trophy. All four were initially asymptomatic (NYHA class I). Three remained asymptomatic, while one developed mild symptoms (NYHA class II). The cardiothoracic ratio increased in only one patient (from 0·51 to 0·57).

Cardiac catheterisation, performed in two of the four patients showed a resting outflow pressure gradient in both (60 and 100 mm Hg respectively). During the follow up period, all four patients were treated with propranolol (80–160 mg/day).

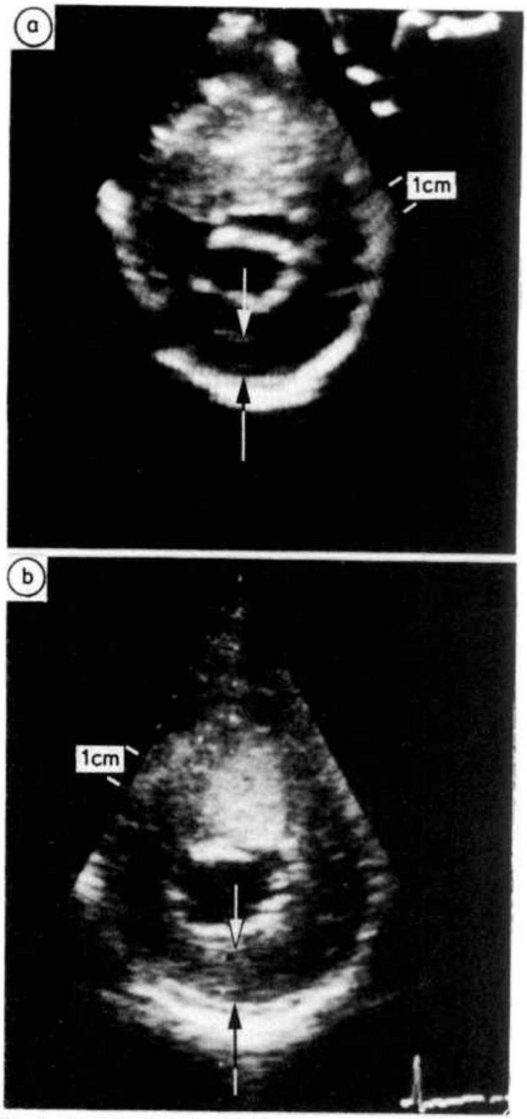

Fig. 5 *End diastolic cross sectional echocardiographic parasternal short axis views at the level of the basal region of a patient with hypertrophic cardiomyopathy showing (a) hypertrophy of the entire interventricular septum and of the inferoposterior segment of the free wall with normal thickness of the anterolateral segment of the free wall, and (b) hypertrophy of the anterolateral segment of the free wall three years later.*

SURGICALLY TREATED GROUP

In the 11 patients who had undergone septal myotomy-myectomy, no progression of hypertrophy was noted on either their cross sectional echocardiograms or electrocardiograms; their clinical status remained unchanged.

Discussion

Our study represents the first observation of progres-

Table 3 *Clinical and electrocardiographic characteristics of the four patients with hypertrophic cardiomyopathy in whom cross sectional echocardiographic follow up showed progression of hypertrophy*

Case No	*Sex/age (yr)*	*Duration of follow up (yr)*	*Family incidence hypertrophic cardiomyopathy*	*NYHA class*		*Treatment with propranolol (mg/day)*	*Electrocardiography*			
							SV1+RV5 (mm)		*Score* (points)*	
				A	*B*		*A*	*B*	*A*	*B*
1	F/53	3	–	I	I	160	64	65	5	5
2	M/49	4	–	I	I	80	40	58	2	5
3	M/49	4	–	I	II	120	40	52	5	8
4	M/17	3	+	I	I	160	46	LBBB	4	LBBB

–, absent; +, present; A, initial evaluation; B, last evaluation; LBBB, left bundle branch block.
*Romhilt-Estes point-score system.[20]

sion of hypertrophy in hypertrophic cardiomyopathy. Electrocardiographic evidence of progression of hypertrophy has been reported by McKenna *et al* in 20% of their patients with hypertrophic cardiomyopathy.[17] The lower proportion of patients with progression of hypertrophy in our study may be explained by the shorter follow up period (3·5 years *vs* 8 years) and by the use of a different diagnostic technique. Indeed, previous studies have shown a poor correlation between the electrocardiographic and M mode echocardiographic changes seen in hypertrophic cardiomyopathy.[22–24] Cross sectional echocardiography, by visualising the cardiac chambers and walls in multiple cross sectional planes and providing accurate information about the distribution of the hypertrophy, is superior to electrocardiography in detecting hypertrophy. Moreover, conduction disturbances, which are a common finding in these patients especially after septal myotomy-myectomy,[14 25] further limit the use of electrocardiography in studying the progression of hypertrophy. In the present study electrocardiography failed to detect the progression of hypertrophy in two of the four patients in whom this was clearly seen by cross sectional echocardiography. The good reproducibility of the cross sectional echocardiograms in identifying the areas of hypertropy in our study is supported by the high rate of agreement obtained by the two observers (98%). These data agree with those of previous similar studies.[15 16] For the assessment of the progression of the hypertrophy, thickness measurements obtained from M mode echocardiograms must be guided by cross sectional echocardiography, thus limiting the variability of these measurements.[26–28]

Age, sex, familial incidence of hypertrophic cardiomyopathy, and medical treatment do not seem to influence the potential progression of hypertrophy. McKenna *et al*, using electrocardiography in a larger patient population, found not relation between these factors and the increase of electrocardiographic indices of left ventricular hypertrophy.[17] These authors noted worsening of symptoms in their patients with

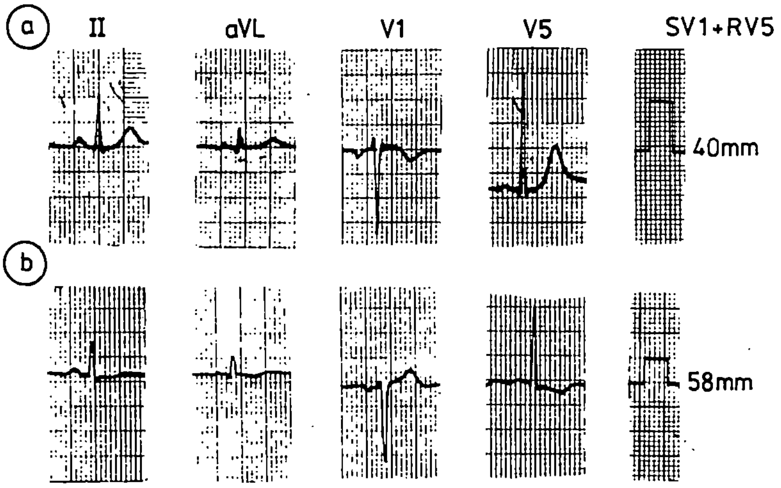

Fig. 6 *Electrocardiograms recorded in (a) 1979 and (b) three years later of a patient with cross sectional echocardiographic evidence of progressive hypertrophy showing a substantial increase in the voltage criteria of left ventricular hypertrophy (note different calibration).*

the increase of hypertrophy, whereas this occurred in only one of our patients.

The absence of progression of hypertrophy in the patients who had had a septal myotomy-myectomy may indicate that in addition to symptomatic improvement[29–31] this intervention may prevent the progression of hypertrophy. This observation obviously needs further confirmation. We stress the importance of standardisation of the cross sectional echocardiographic evaluation of patients with hypertrophic cardiomyopathy. This would allow a better comparison between different studies, should greatly increase our knowledge about the morphological aspects of hypertrophic cardiomyopathy, and further determine the rate and clinical importance of the progression of hypertrophy in this disease.

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Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia

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SUMMARY The effect of amiodarone on survival was assessed in patients with hypertrophic cardiomyopathy and ventricular tachycardia in a drug trial with historical controls. During 1976 and 1977, 24 hour (seven) or 48 hour (79) electrocardiographic monitoring was performed in 86 consecutive patients; 24 had ventricular tachycardia and received conventional antiarrhythmic agents. Nineteen clinical, echocardiographic, and haemodynamic features were assessed. Seven patients died suddenly during follow up of three years; of these, five had continued to have ventricular tachycardia and two had no documented ventricular tachycardia. During 1978 and 1979, ventricular tachycardia was detected during 48 hour electrocardiographic monitoring in 21 of the next 82 consecutive patients with hypertrophic cardiomyopathy. They received amiodarone (150–400 mg/day, median 300); ventricular tachycardia was suppressed in all during repeat 48 hour electrocardiographic examination. Two patients died suddenly during a three year follow up, but neither belonged to the amiodarone treated group with ventricular tachycardia. The clinical and haemodynamic variables were similar in patients taking amiodarone and conventional agents. The fact that control of ventricular arrhythmia with amiodarone is significantly associated with improved survival suggests that amiodarone may prevent sudden death in patients with hypertrophic cardiomyopathy and ventricular tachycardia.

The high risk of sudden death was one of the earliest recognised features and is the most important problem in the management of patients with hypertrophic cardiomyopathy.[1–6] Approximately 25% of patients show bursts of ventricular tachycardia during electrocardiographic monitoring, and they are at even greater risk.[7–11] Amiodarone has been available in the United Kingdom since 1973, initially for use on compassionate grounds in specified patients with refractory arrhythmia. Once its efficacy was demonstrated[12 13] we have since 1978 extended its use to patients with hypertrophic cardiomyopathy and ventricular arrhythmia.[14] We now report our experience of the effect of amiodarone on survival of patients with hypertrophic cardiomyopathy and ventricular tachycardia. We compared the three year survival of 24 consecutive patients with ventricular tachycardia who had been treated initially with conventional antiarrhythmic agents and of the next 21 consecutive patients with ventricular tachycardia, who received amiodarone.

Patients

One hundred and sixty eight consecutive patients with hypertrophic cardiomyopathy aged ≥5 years who were seen at this hospital during 1976 to 1979 underwent ambulatory electrocardiographic monitoring with no cardioactive treatment other than beta adrenergic blockers, verapamil, or digoxin. Hypertrophic cardiomyopathy is defined as a heart muscle disorder of unknown origin that is characterised by unexplained hypertrophy of a non-dilated left ventricle.[15] The diagnosis was confirmed in 158 patients by the demonstration of unexplained left ventricular hypertrophy during cross sectional echocardiography. The pattern of hypertrophy was classified as asym-

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metrical, symmetrical, or predominantly distal ventricular.[15] In the remaining patients echocardiography was technically difficult and the diagnosis relied on clinical, haemodynamic, and angiographic features.[4] No patient had documented systemic hypertension. Cardiac catheterisation had been performed in 142 patients, in 112 of them within three years of the study. Patients were considered to have a left ventricular gradient if the difference under basal conditions or after provocation was ≥30 mm Hg.

Methods

During 1976 and 1977 ventricular tachycardia, defined as ≥3 consecutive ventricular extrasystoles with a mean rate of >120 beats/minute, was detected in two of seven patients who underwent 24 hour electrocardiographic monitoring and in 22 of 79 who underwent 48 hour electrocardiographic monitoring. Details of these 86 patients have been published.[10] Symptomatic treatment in the 24 with ventricular tachycardia included propranolol in 15 (63%), diuretics in four (17%), and verapamil in one (4%). They received disopyramide 400–800 mg daily, mexiletine 600 mg daily, or quinidine 500 mg daily; eight received two of these drugs and one was given all three. Treatment was guided by electrocardiographic monitoring and the presence or absence of side effects; plasma drug concentrations were not measured. Ventricular tachycardia was suppressed in five of the 24.

During 1978 and 1979, 21 of the next 82 patients had ventricular tachycardia during 48 hour electrocardiographic monitoring. Symptomatic treatment in these 21 included propranolol in 16 (76%), diuretics in seven (33%), and verapamil in two (10%). They received amiodarone 400–1200 (mean 800) mg daily for one week followed by 200 or 400 mg daily for the initial maintenance period (four weeks). The dose was then adjusted 1–7 (median 2) times during the three years in an attempt to achieve the minimum effective maintenance dose. Details of their management, particularly of the relation of dose, plasma drug concentration, efficacy, and side effects, have been published.[16] In brief, plasma amiodarone concentrations were appropriate for the daily dose, and none of these 21 patients experienced serious side effects. Ventricular tachycardia was suppressed with 150–400 (median 300) mg daily.

The consecutive patient populations with ventricular tachycardia were compared using 19 clinical, echocardiographic, and haemodynamic variables; their survival was assessed during an outpatient visit and was compared 36 months after the detection of ventricular tachycardia using Fisher's exact test and life table analysis.[17] Death was defined as sudden if it was unexpected and instantaneous. No patient was lost to follow up.

Results

The mean and maximum rate and duration of ventricular tachycardia were similar in the two treatment groups; the incidence of associated ventricular and supraventricular arrhythmias was marginally higher in the amiodarone group (Table 1). There were no significant differences in clinical, prognostic, echocardiographic, or haemodynamic features between the two groups (Tables 2 and 3).

Of patients with ventricular tachycardia, five of 24 who were treated with conventional antiarrhythmic drugs died suddenly and unexpectedly within three years, whereas all 21 who received amiodarone survived three years or longer (Fig. 1). Treatment with amiodarone was associated with improved survival ($p<0{\cdot}04$). The overall mortality in patients who did not have ventricular tachycardia was similar during

Table 1 *Arrhythmias in two consecutive groups of patients with ventricular tachycardia treated with conventional antiarrhythmic agents or amiodarone. Figures are numbers (percentages)*

	Conventional agents (n=24)	*Amiodarone (n=21)*
Atrial fibrillation	3 (13)	3 (14)
Supraventricular tachycardia or paroxysmal atrial fibrillation	9 (43)	13 (68)
>200 ventricular extrasystoles/day	12 (50)	11 (52)
Multiform and paired ventricular extrasystoles	19 (79)	19 (90)
Rate of ventricular tachycardia/min:		
Maximum	210	190
Mean	142	146
Beats of ventricular tachycardia:		
Maximum	27	22
Mean	8	7

Table 2 *Clinical and prognostic features in patients with ventricular tachycardia treated with conventional agents or amiodarone. Figures are numbers (percentages) of patients unless stated otherwise*

	Conventional agents (n=24)	*Amiodarone (n=21)*
Mean (SD) age (yr)	46 (12)	44 (13)
Mean (SD) follow up (yr)	6 (5)	7 (7)
Mean (SD) duration of symptoms (yr)	9 (8)	8 (7)
Male	16 (67)	14 (67)
Female	8 (33)	7 (33)
Family history of hypertrophic cardiomyopathy and sudden death	5 (21)	3 (14)
Syncope	5 (21)	8 (38)
Severe dyspnoea	5 (21)	6 (29)
Chest pain	10 (43)	10 (48)

Table 3 *Echocardiographic and haemodynamic features in patients with ventricular tachycardia treated with conventional agents or amiodarone. Figures are numbers (percentages) of patients unless stated otherwise*

	1976–77 (n=24)	*1978–79 (n=21)*
Asymmetrical septal hypertrophy	10 (43)	8 (38)
Symmetrical left ventricular hypertrophy	10 (43)	11 (52)
Mean (SD) thickness of thickest segment (mm)	22 (6)	21 (4)
Left ventricular gradient ≥30 mm Hg	11 (50)	10 (50)
Mean (SD) left ventricular end diastolic pressure (mm Hg)	19 (6)	17 (7)

the earlier and later treatment periods (two of 62 and three of 61 respectively).

Discussion

Approximately one third of patients with hypertrophic cardiomyopathy die suddenly within 10 years of diagnosis.[5 6] Children and those with a family history of hypertrophic cardiomyopathy and sudden death, previous syncopal episodes, or ventricular tachycardia during electrocardiographic monitoring are at particular risk.[2–6 10 11] In this study of adults with hypertrophic cardiomyopathy and ventricular tachycardia there was a 21% three year mortality from sudden death in the 24 patients who were treated with conventional antiarrhythmic drugs compared with no deaths among the next 21 consecutive patients who took amiodarone, all of whom survived at least three years (Figure 2). Though conventional antiarrhythmic agents may in theory increase the incidence of sudden death,[18] we did not observe putative mechanisms for this, for example, QT prolongation or multiform ventricular tachycardia. Overall, therefore, we interpret these results as suggesting that amiodarone may prevent sudden death in these high risk patients.

For historical reasons this comparison of survival during treatment with conventional antiarrhythmic drugs and amiodarone could not be randomised but was based on two consecutive patient populations with hypertrophic cardiomyopathy who had ventricular tachycardia detected during electrocardiographic monitoring. Soon after our recognition of the high incidence of ventricular arrhythmia we entered seven of the patients with ventricular tachycardia (included in the conventional treatment group) into a comparative study of the antiarrhythmic effect of disopyramide and mexiletine. Arrhythmias were not controlled, side effects were common, and four of the seven died suddenly during treatment. Amiodarone had just received a restricted licence in the United Kingdom; it was quickly shown to be an effective antiarrhythmic agent in these patients,[14] and a randomised prospective study in patients with hypertrophic cardiomyopathy and ventricular tachycardia was never feasible. To date no patient has died suddenly while taking amiodarone either in this comparative series of patients with ventricular tachycardia or in our larger series of patients with hypertrophic cardiomyopathy and other arrhythmias.[16] It would not now be possible for us to justify a randomised prospective study of amiodarone and conventional antiarrhythmic agents in patients with hypertrophic cardiomyopathy and ventricular tachycardia.[19]

The characteristics of these two consecutive patient populations with hypertrophic cardiomyopathy and ventricular tachycardia were comparable. Clinical and prognostic features, the extent and distribution of left ventricular hypertrophy, left heart filling pressures, and the proportion of patients with left ventricular gradients were similar in the two groups. The characteristics of the episodes of ventricular tachycardia were also similar in patients who received conventional antiarrhythmic drugs and those who received amiodarone, while the incidence of associated supraventricular and ventricular arrhythmias was not

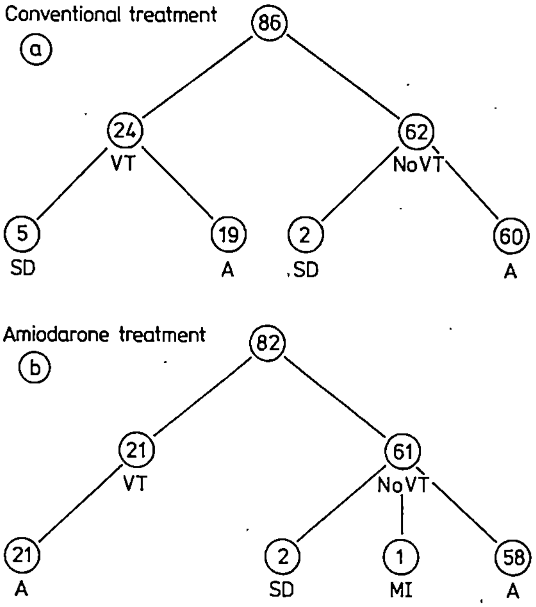

Fig. 1 *Clinical outcome (a) in 86 consecutive patients undergoing electrocardiographic monitoring during 1976 and 1977, of whom 24 with ventricular tachycardia (VT) were treated with conventional antiarrhythmic drugs; and (b) in 82 consecutive patients undergoing electrocardiographic monitoring during 1978 and 1979, of whom 21 with ventricular tachycardia (VT) were treated with amiodarone. SD, sudden death; A, alive; MI, died of documented myocardial infarction.*

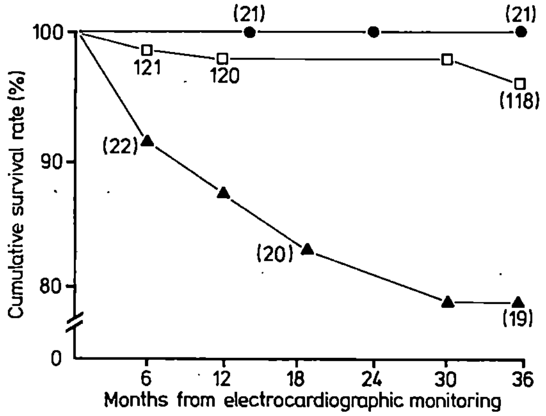

Fig. 2 *Cumulative survival rate for 24 patients with ventricular tachycardia treated with conventional antiarrhythmic agents (▲), 21 with ventricular tachycardia treated with amiodarone (●), and 123 without ventricular tachycardia (□). The probability of cardiac death is equal to the total number of deaths for the year divided by the adjusted number at risk minus the number of deaths due to other causes.*[17]

significantly greater in the latter group. In the only other large series, from the National Institutes of Health, four of 17 patients with ventricular tachycardia, who received conventional antiarrhythmic agents, died suddenly or experienced cardiac arrest during three years[11]; thus the annual mortality from sudden death of 8·6% was similar to our own finding in these patients with ventricular tachycardia. The annual mortality from sudden death in medically treated patients without ventricular tachycardia was also similar in the National Institutes of Health series (two of 66) and in our two consecutive populations (two of 62; and two of 61). During the period of the study we used the same approach to the treatment of symptoms, and we corroborated the fact that our referral sources, diagnostic criteria, and indications for electrocardiographic monitoring did not alter.

Of the many potential causes of sudden death in hypertrophic cardiomyopathy, primary ventricular arrhythmia and acute reduction in left ventricular volume from decreased afterload or filling pressure are the most likely to be important. Amiodarone does not alter systolic or diastolic blood pressure or radionuclide indices of left ventricular function,[20] so it is logical to assume that amiodarone prevents sudden death through suppression of episodes of ventricular arrhythmia. It is also possible that an unfavourable haemodynamic alteration is the initiating event and that the clinical outcome is determined by the electrical behaviour of the myocardium. If this hypothesis is correct amiodarone may be effective not so much by suppressing non-sustained episodes of ventricular tachycardia as by promoting electrical stability of the myocardium[21] and may warrant evaluation in other high risk patients with hypertrophic cardiomyopathy.

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Ventricular arrhythmias
A guide to their localisation

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SUMMARY An electrocardiographic atlas of ventricular tachycardias was produced by pacing 27 epicardial sections of the heart and the mitral papillary muscles to simulate focal ventricular arrhythmias and simultaneously recording their 12 lead electrocardiographic appearances. One hundred and twenty nine patients undergoing cardiac surgery were studied. In five patients all 27 epicardial sites were paced at operation and in 124 individual sections were paced postoperatively with temporary epicardial wires and the electrocardiograms analysed in terms of frontal and horizontal plan QRS axis, maximum limb lead QRS amplitude, and QRS duration. Each ventricular region paced produced a distinctive 12 lead electrocardiographic pattern.

Simulated right ventricular arrhythmias had either inferior frontal plane QRS axes (from the anterobasal region) or superior frontal plane QRS axes (from the apical and posterior right ventricular sections). Horizontal plane QRS axes were directed leftwards, with some posterior shift in the anteroapical regions. Simulated arrhythmias from the base of the left ventricle (anteriorly and laterally) had inferior frontal plane QRS axes and anterorightward horizontal plane QRS axes. Left ventricular arrhythmias with a superior frontal plane QRS axis were readily distinguished by their horizontal plane QRS axes: posterorightwards from the anterior and anterorightwards from the posterior left ventricular sections. Standard errors of the paced QRS axes for the various epicardial sections paced postoperatively ranged from 3·0° to 6·0° using the frontal plane axis. The electrocardiogram was most accurate in localising ventricular arrhythmias from the anterior left ventricle and least accurate for those arising from the inferior right ventricle. The appearance of the paced electrocardiograms was slightly modified by underlying disease such as myocardial infarction and left ventricular hypertrophy.

This atlas may be useful in comparing the localisation of ventricular tachycardia with the site of underlying cardiac disease and may facilitate mapping in patients with refractory ventricular tachycardia requiring ablation (either surgical or by high energy impulses).

Deductive electrocardiography allows approximate localisation of ventricular arrhythmias using the principles of axis analysis with its inherent limitations. An alternative method of localising ventricular tachycardia from the conventional 12 lead electrocardiographic appearances is by a direct comparison with arrhythmias arising from known sites—that is, from an atlas of ventricular arrhythmias.

An atlas can be produced by pacing several selected parts of the heart to mimic ventricular tachycardia. The surface electrocardiographic appearances resulting from ventricular stimulation at different sites were first investigated by Kraus and Nicolai in 1907.[1] Shortly after this, Lewis noted the similarity between the electrocardiographic appearances produced by stimulating the right and left ventricles and those obtained from cutting the left or right bundle branches respectively.[2–4] Oppenheimer and Stewart in 1926,[5] Barker *et al* in 1930,[6] and Abramson *et al* in 1937[7] furthered the knowledge in this field, but it was with the advent of more sophisticated electrophysiological techniques that later workers showed that pacing the site of earliest ventricular activation

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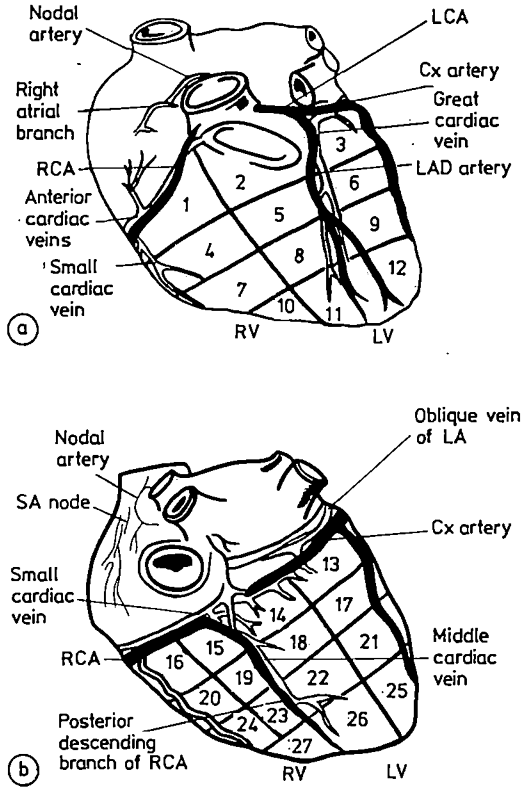

Fig. 1 *Diagram of the anterior and posterior ventricular epicardium divided into 27 sections, 12 anteriorly and 15 posteriorly in (a) the sternocostal aspect and (b) the diaphragmatic aspect. RCA, right coronary artery; LCA, left coronary artery; Cx, circumflex; LAD, left anterior descending; SA, sinoatrial; LA, left atrium; RV, right ventricle; LV, left ventricle.*

reproduces very closely the QRS morphology of the spontaneous tachycardia under investigation.[8–10] In this study we used this technique of pace mapping, which was adopted initially to localise ventricular tachycardia during surgery,[11] to produce an electrocardiographic atlas of ventricular arrhythmias arising from certain surfaces of the heart but not as yet of those arising from the His-Purkinje trunk and its main branches.

Patients and methods

The electrocardiographic appearances of ventricular arrhythmias were recorded in two separate studies.

VENTRICULAR ARRHYTHMIAS FROM DIFFERENT SITES IN THE SAME PATIENT (OPEN CHEST)

Five patients undergoing cardiac surgery for the management of their valvar or ischaemic heart disease were included in this study. None of the patients with ischaemic heart disease had had a myocardial infarction. At open heart surgery, the ventricular epicardium was considered to consist of 27 sections (Fig. 1), 12 anterior sections (eight right ventricular and four left ventricular) and 15 posterior sections (seven right ventricular and eight left ventricular). The heart was paced from each section using a small bipolar electrode (Plastimed, Paris) with 4 mm between poles. This electrode could be attached to the appropriate section and the heart returned to its normal position within the thorax during the brief period of ventricular pacing mostly at heart rates between 100 and 150 beats/min, which were constant for each patient. Pacing was performed at 1·0 V above threshold values, usually 2·0–3·0 V. During ventricular pacing the electrocardiogram was recorded to document the characteristic appearances of arrhythmias arising from each section, as represented in the six standard limb leads and three atypical chest leads, V4R, V5, and V6 (all in the open thorax). The electrocardiograms were recorded during inspiration and expiration.

VENTRICULAR ARRHYTHMIAS FROM THE SAME SITE IN DIFFERENT PATIENTS (CLOSED CHEST)

In 124 adult patients undergoing heart surgery a temporary pacing wire was inserted to produce focal activation of one of the 27 epicardial sections (Fig. 1). In many patients the surgeons found sections 10 and 11 difficult to distinguish during implantation of the temporary epicardial wires, and these regions were considered as one. The same problem occurred with sections 15 and 16 on the posterior right ventricle, which were also regarded as one.

The temporary pacing wires used have a small exposed section of wire approximately 2–3 cm distal to the introducing needle. The pacing wire was inserted via the ventricular epicardium as a single stitch, until the exposed section was buried immediately below the epicardium, leaving the two ends of the wire protruding. This gave a well localised pacing stimulus. The wire was sutured on to the epicardium so that it did not become detached in the early postoperative period yet was easily removed at the end of the pacing study. The leads of the temporary epicardial wires were brought out by a separate incision and the chest closed in the usual manner. Five to seven days postoperatively the wires were paced using a Devices box at a rate of 10 beats/min above the patient's resting rate and a voltage 1·0 V above the threshold voltage. A 12 lead electrocardiogram was recorded during pacing with the patient supine and during quiet respiration.

In five patients this technique was also used to define the 12 lead electrocardiographic appearances of

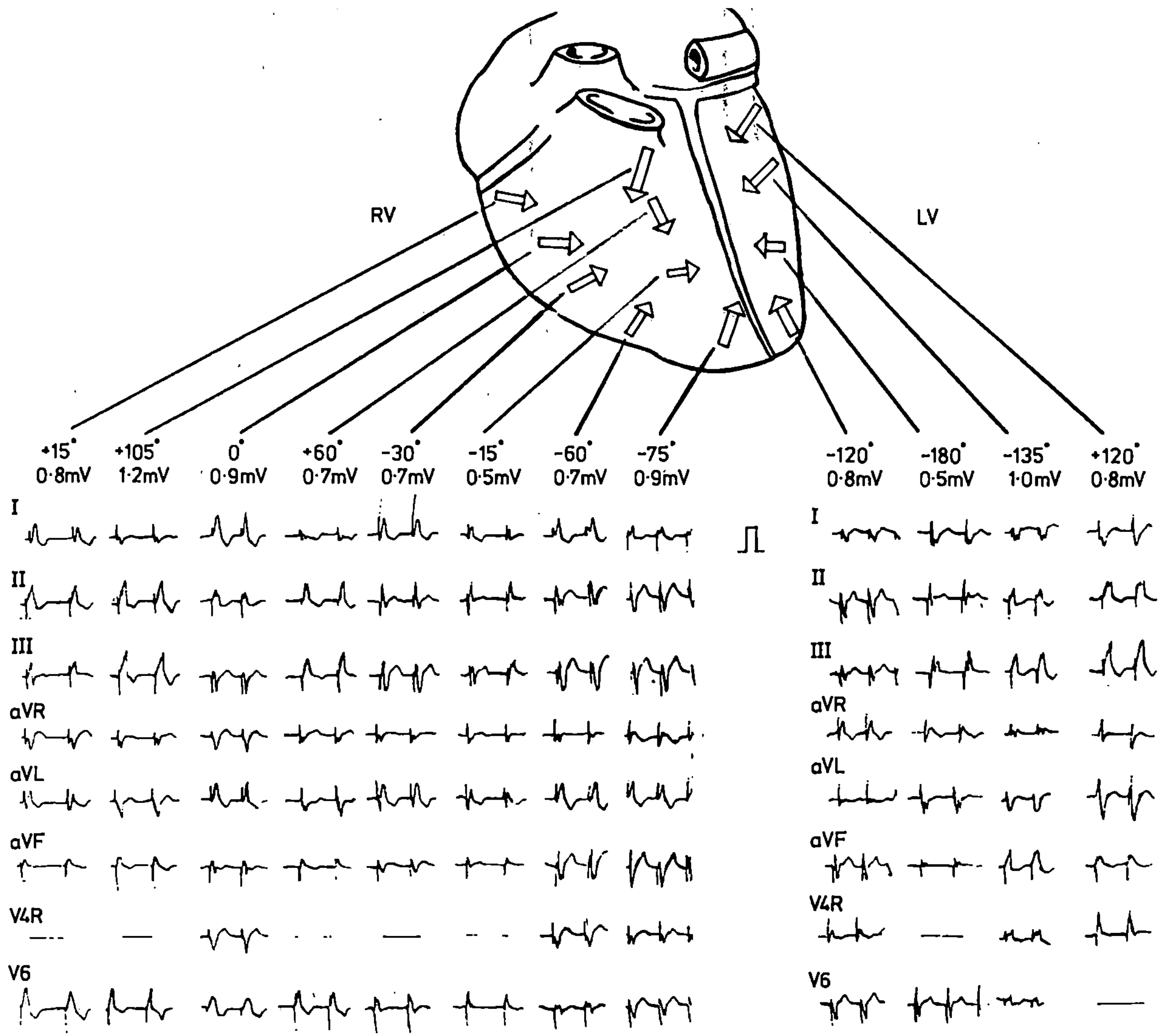

Fig. 2 *Electrocardiographic appearances (eight leads) obtained by pacing the anterior ventricular epicardial sections in one patient directly during operation. The arrows summarise the limb lead QRS complexes: their direction represents the limb lead QRS axis, their length indicates the mean maximum QRS amplitude, and their width the QRS duration. RV, right ventricle, LV, left ventricle.*

Table 1 *Results of electrocardiograms produced on pacing the anterior and posterior ventricles at operation*

Section	*No of patients*	*Limb lead QRS axis*			*Maximum limb lead QRS amplitude (mV)*			*QRS duration (s)*
		Mean	*Range*	*SE*	*Mean*	*Range*	*SE*	
				Anterior ventricles				
Right:								
1	5	+15°	0° to +30°	4·74°	0·96	0·80–1·0	0·02	0·12
2	5	+99°	+90° to +105°	3·67°	1·08	1·0–1·2	0·04	0·12
4	5	−6°	0° to −15°	3·67°	0·97	0·8–1·1	0·05	0·12
5	5	+63°	+45° to +75°	5·6°	0·82	0·7–0·9	0·04	0·12
7	5	−42°	−30° to −60°	5·6°	0·94	0·7–1·1	0·05	0·12
8	5	−6°	0° to −15°	3·67°	0·56	0·4–0·8	0·07	0·10
10/11	5	−69°	−60° to −75°	3·67°	0·96	0·8–1·1	0·04	0·12
Left:								
3	5	+129°	+120° to +135°	3·67°	1·07	0·8–1·3	0·09	0·12
6	5	+142°	+135° to +150°	3·67°	1·04	0·8–1·3	0·09	0·12
9	5	−171°	−150° to −180°	6·0°	0·60	0·5–0·7	0·03	0·10
12	5	−139°	−120° to −150°	4·74°	0·80	0·7–1·0	0·05	0·12
				Posterior ventricles				
Right:								
15/16	5	−9°	0° to −30°	6·0°	0·94	0·8–1·0	0·02	0·12
19	5	−33°	−15° to −45°	5·6°	0·69	0·5–0·8	0·03	0·12
20	5	−30°	−15° to −45°	4·74°	0·78	0·7–0·9	0·04	0·12
23	5	−63°	−60° to −75°	3·0°	0·9	0·7–1·0	0·03	0·12
24	5	−54°	−45° to −60°	3·67°	0·76	0·6–0·9	0·05	0·12
27	5	−93°	−75° to −105°	5·6°	1·08	1·0–1·2	0·04	0·12
Left:								
13	5	+159°	+150° to +165°	3·67°	0·96	0·8–1·1	0·05	0·12
14	5	−45°	−30° to −60°	4·74°	0·88	0·8–1·0	0·04	0·12
17	5	−147°	−135° to −165°	5·6°	0·84	0·6–1·0	0·06	0·12
18	5	−57°	−45° to −60°	3·0°	1·08	0·9–1·2	0·06	0·12
21	5	−141°	−135° to −150°	3·67°	0·88	0·7–1·0	0·05	0·12
22	5	−78°	−60° to −90°	5·6°	1·12	1·0–1·2	0·04	0·11
25/26	5	−108°	−90° to −120°	5·6°	1·08	0·9–1·2	0·04	0·12

ventricular arrhythmias arising from the mitral valve papillary muscles. The temporary pacing electrode was inserted from the endocardial aspect into the papillary muscle and the lead drawn through to the epicardial surface until the bared active tail of the electrode was left in the papillary muscle below the surface in its muscular body. The electrodes were fixed by a small epicardial suture to prevent migration of the electrode tip.

The temporary electrodes were removed after one week by simple traction without complication, and as such was a simple modification of the routine practice of leaving a temporary epicardial electrode after open heart surgey to overcome any episodes of bradycardia that may complicate the early postoperative period.

Patients

The electrocardiographic appearances of between four and seven patients were recorded per site (mean 4·98 patients/site). The 124 patients included in this study were aged between 16 and 64 years; 68 were men and 56 women. Eighty nine (71·7%) had ischaemic heart disease, 38 of whom had had previous myocardial infarction, and 27 (21·7%) valvar heart disease. Of the latter group, 10 underwent aortic valve replacement, 10 mitral valve replacement, and seven replacement of both valves. A further four patients required surgery for valvar and coronary artery disease, two had repair of secundum atrial septal defects, one repair of a ventricular septal defect, and one section of a left side Kent pathway (with an otherwise normal heart).

The five patients in whom pacing of the mitral valve papillary muscles was performed were aged 50–66 years; three were men and two women undergoing mitral valve replacement, three for predominant mitral regurgitation and two for mixed mitral valve disease.

No patient had spontaneous ventricular tachycardia or a left ventricular aneurysm. None was undergoing repeat coronary artery bypass grafting.

ASSESSMENT OF ELECTROCARDIOGRAPHIC APPEARANCES

Paced QRS complexes from ventricular activation were described in terms of the following features: (*a*) frontal plane QRS axis; (*b*) horizontal plane QRS axis; (*c*) maximum limb lead QRS amplitude; and (*d*) QRS duration. The frontal plane axis of the main QRS deflection was calculated conventionally by reference to all six limb leads. A final correction of +15° or −15° was made if the original calculation was based on a lead whose deflection was not completely equiphasic. The horizontal plane QRS axis was similarly calculated by reference to all precordial leads and

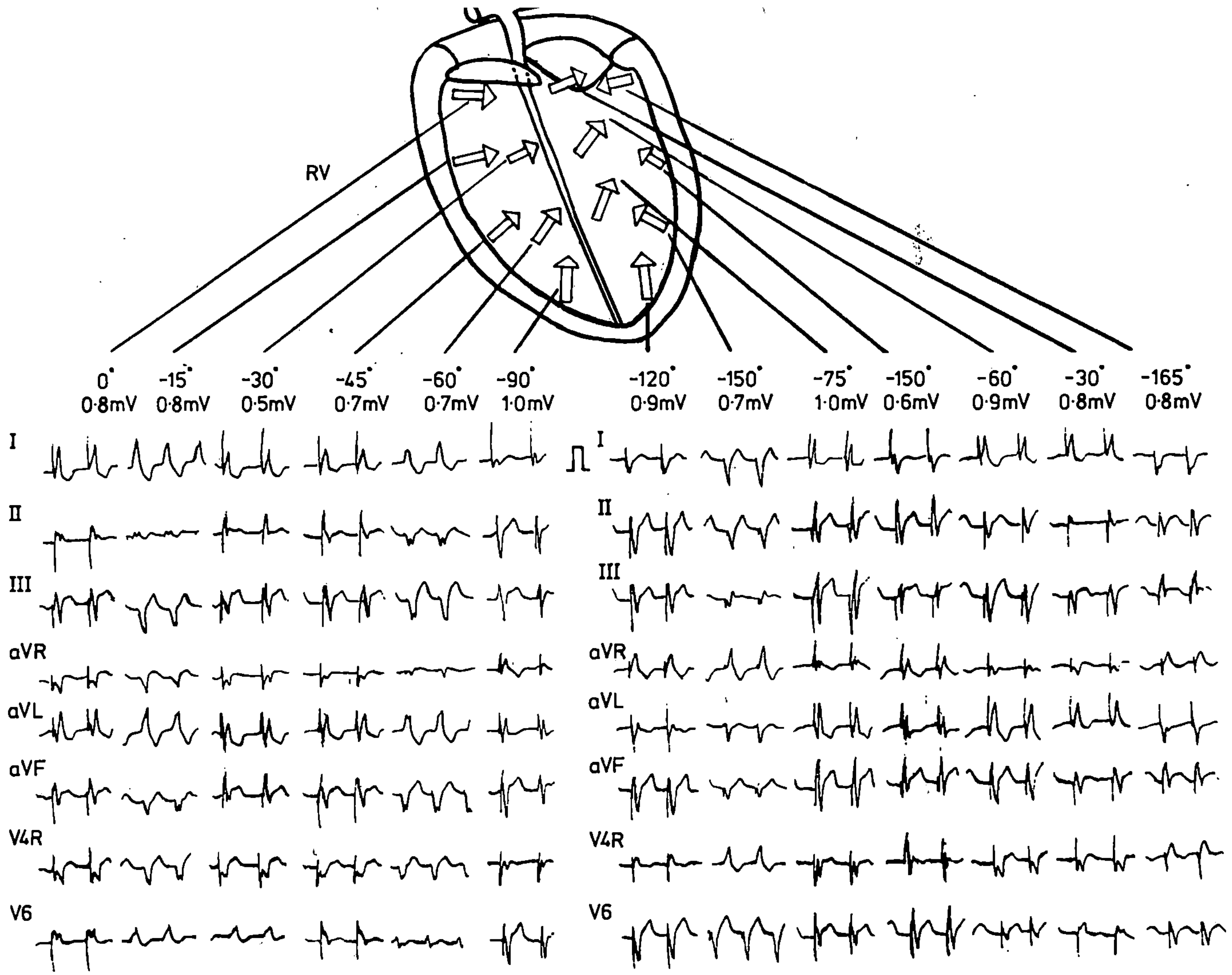

Fig. 3 *Electrocardiographic appearances (eight leads) obtained by pacing the posterior ventricular epicardial sections, again in one representative patient, directly during surgery. The arrows summarise the limb lead QRS appearances as in Fig. 2.*

was at right angles to that precordial lead showing the most equiphasic deflection. Each feature was influenced by the site of ventricular activation and is represented diagrammatically by an arrow that has direction, length, and width (QRS axis, amplitude, and duration respectively) in subsequent Figures.

Results

OPEN CHEST STUDY

Anterior ventricles—Figure 2 shows the representative electrocardiographic appearances in the six limb leads and two precordial leads produced by direct epicardial stimulation of the anterior ventricles in five patients. Pacing the right ventricular outflow tract produced a limb lead QRS axis of +105°. Moving the site of stimulation closer to the right ventricular apex produced an anticlockwise swing in the limb lead QRS axis, such that paced arrhythmias from the apex had a frontal plane QRS axis of −75°. Changes in QRS amplitude also occurred, amplitude being greatest when the ventricles were activated from their poles (apex and base) and smallest in sections 8 and 9 (Fig. 1) adjacent to the interventricular septum, an electrocardiographic low amplitude centre of the ventricles. Pacing the left ventricular epicardial sections immediately adjacent to the left anterior descending coronary artery changed the limb lead QRS axis from +120° at the base to −120° at the apex, a clockwise swing of 120°. Again a reduction then restoration of the QRS amplitude occurred. Table 1 shows the details of the limb lead QRS axes in all five patients. The QRS duration of simulated ventricular arrhythmias was narrowest (mean 0·10 s, sections 8 and 9) near the septum, especially in the mid zones anteriorly, and widest laterally.

Posterior ventricles—Figure 3 shows representative electrocardiograms produced by epicardial stimulation of the posterior ventricles. Pacing the posterior right ventricular base produced a limb lead QRS axis of 0°. Moving the pacing site nearer to the posterior right ventricular apex via the free wall again produced a stepwise anticlockwise swing in axis to −90°. A similar trend was produced on pacing those posterior left ventricular sections adjacent to the interventricular septum. Pacing the remaining left ventricular sections altered the limb lead QRS axis from +165° at the base to −120° at the apex (Table 1). There was a slight tendency to a reduction in QRS amplitude at the mid sections of the posterior ventricles, but no definitive picture emerged of an electrocardiographic low amplitude centre as was apparent anteriorly. The duration of paced QRS complexes of simulated ventricular arrhythmias was 0·11–0·12 s. Increasing the pacing rate or pacing energy produced no appreciable changes in the QRS morphology.

Changes in ventilation during pacing produced slight alteration in the limb lead QRS morphology only at maximum inspiration and expiration in two patients. Deeper S waves were present in leads I and aVL on maximum inspiration than on expiration. Therefore pacing as described in the methodology for open chest patients was performed only during normal respiration. The three precordial leads V4R, V5, and V6 recorded with the chest open were only sufficient to determine the bundle branch block pattern and added little further localising information.

CLOSED CHEST STUDY

Table 2 summarises the appearances of the limb lead QRS complexes produced on pacing the ventricular epicardial sections in the 124 patients in the second study.

Anterior ventricles—Pacing the right ventricular outflow tract produced a mean limb lead QRS axis of +75° changing to a mean value of +51°, −12°, and −66° as the right ventricle was paced stepwise from outflow to apex in a line parallel to the interventricular septum. A similar anticlockwise swing was present in the remaining anterolateral right ventricular sections. Pacing the anterior left ventricular apex produced a mean limb lead QRS axis of −153° with a mean maximum limb lead QRS amplitude of 0·7 mV. As the pacing site was moved upwards the anticlockwise swing of the QRS axis continued, ending in a mean limb lead QRS axis of +123° at the left ventricular outflow tract, encompassing an arc of almost 360°. Figure 4 shows electrocardiograms from individual patients, and the tracings are representative of the results obtained on pacing the same section in different patients. Complexes of minimum amplitude and duration were encountered in positions 5, 8 (right ventricle), and 9 (left ventricle), again giving rise to an electrocardiographic "centre" to the map. Crossing the interventricular septum from right to left was associated with the development of a small R wave in lead V1 equivalent in conventional terminology to a transition from left to right bundle branch block appearances. The differences in limb lead axes between Figs. 2 (first study) and 4 (second study) are probably due to inconsistencies in electrode placement. Figure 5 summarises the precordial lead QRS axes produced on pacing the anterior ventricular sections.

Posterior ventricles—The limb and precordial lead complexes obtained on pacing the posterior ventricular sections can be analysed in the same way and their appearances are shown in Table 2 and Fig. 6. Pacing the posterior right ventricular apex produced a mean limb lead QRS axis of −81°, which swung anticlockwise to mean values of −63°, −42°, and −7·5° as the pacing site was moved stepwise up to the base of the heart adjacent to the posterior interventricular sep-

Table 2 *Results of electrocardiograms produced on pacing anterior and posterior ventricles postoperatively*

Section	*No of patients*	*Limb lead QRS axis*			*Maximum limb lead QRS amplitude (mV)*			*QRS duration (s)*
		Mean	*Range*	*SE*	*Mean*	*Range*	*SE*	
				Anterior ventricles				
Right:								
1	5	+9°	0° to +15°	3·67°	0·88	0·7–1·2	0·08	0·12
2	5	+75°	+60° to +90°.	4·74°	1·28	1·1–1·5	0·07	0·12
4	5	−21°	0° to −30°	6·0°	0·84	0·7–1·1	0·09	0·12
5	5	+51°	+45° to +60°	3·67°	0·62	0·5–0·7	0·05	0·10
7	5	−39°	−30° to −45°	3·67°	1·62	1·1–2·0	0·27	0·12
8	5	−12°	0° to −15°	3·0°	0·65	0·4–0·9	0·10	0·10
10/11	5	−66°	−60° to −75°	3·67°	1·4	1·0–1·7	0·14	0·12
Left:								
3	5	+123°	+120° to +135°	3·0°	1·66	1·3–1·9	0·10	0·12
6	5	+153°	+150° to +165°	3·0°	1·0	0·8–1·2	0·07	0·12
9	5	−177°	−165° to −180°	3·0°	0·5	0·3–0·7	0·04	0·10
12	5	−153°	−150° to −165°	3·0°	0·74	0·5–0·9	0·05	0·12
				Posterior ventricles				
Right:								
15/16	4	−7·5°	0° to −15°	4·3°	1·07	0·7–1·3	0·13	0·12
19	5	−42°	−30° to −45°	3·0°	1·32	0·8–1·9	0·15	0·12
20	5	−36°	−30° to −45°	3·67°	1·58	0·8–2·4	0·32	0·12
23	5	−63°	−60° to −75°	3·0°	1·5	0·8–2·0	0·23	0·12
24	5	−51°	−45° to −60°	3·67°	1·9	1·7–2·5	0·15	0·12
27	7	−81°	−75° to −90°	3·0°	2·2	1·5–3·0	0·33	0·12
Left:								
13	4	+124°	+120° to +135°	3·75°	0·95	0·8–1·1	0·06	0·12
14	4	−49°	−45° to −60°	3·75°	1·55	1·0–2·0	0·29	0·12
17	5	−144°	−135° to −150°	3·67°	0·82	0·5–1·4	0·16	0·12
18	5	−69°	−60° to −75°	3·67°	1·08	0·8–1·7	0·16	0·12
21	5	−129°	−120° to −135°	3·67°	0·94	0·7–1·4	0·12	0·12
22	5	−81°	−75° to −90°	3·67°	1·58	1·3–2·0	0·14	1·12
25	5	−117°	−105° to −120°	3·0°	1·34	0·8–1·9	0·2	0·12
26	5	−93°	−90° to −105°	3·0°	1·68	1·4–2·3	0·16	0·12

tum. Similar frontal plane axes were seen on pacing the left ventricular sections adjacent to the interventricular septum. The remaining left ventricular sections produced a sort of "mirror image" in which the mean limb lead QRS axis swung anticlockwise stepwise from −117° to +124° from apex to atrioventricular groove. A region of low voltage complexes was not found posteriorly, which contrasts with the findings on pace mapping the anterior ventricles. Figure 7 shows the horizontal plane QRS axes. Posterior left ventricular sites could be distinguished from anterior left ventricular sites by reference to the horizontal plane axes.

The appearances obtained in this study using the temporary epicardial wires for postoperative pacing produced results very similar to those of the first study.

Mitral valve papillary muscles

Pacing the anterior papillary muscle of the mitral valve produced a mean limb lead QRS axis of −170° and maximum limb lead QRS amplitude of 1·17 mV, with a mean duration of 0·127 s. The corresponding values produced by pacing the posterior papillary muscle of the mitral valve were −90°, 1·05 mV, and 0·12 s respectively (Table 3, Figs. 8 and 9).

Variation between patients

Pacing the same site in different patients often produced similar 12 lead electrocardiographic appearances despite the wide differences in their physical features and those of their resting 12 lead electrocardiogram in sinus rhythm.

Effects of pre-existing cardiac disorders

Myocardial infarction—Thirty eight of 124 patients in whom temporary epicardial wires were paced postoperatively had previous myocardial infarction. Sixteen patients had had previous anterior myocardial infarction, 20 previous inferior infarction, and two previous posterior myocardial infarction. The presence of inferior myocardial infarction made no appreciable difference to the paced electrocardiograms. Previous anterior or posterior infarctions did not appreciably affect the limb lead appearances of the paced electrocardiograms but principally altered those of the precordial leads. Previous anterior myocardial infarction caused a diminution of the initial R wave amplitude in the precordial leads of the paced complexes, whereas a previous posterior myocardial infarction increased the height of the paced precordial lead R wave. The loss of initial R waves can be seen in Fig. 6, section 19, where the electrocardiogram was recorded

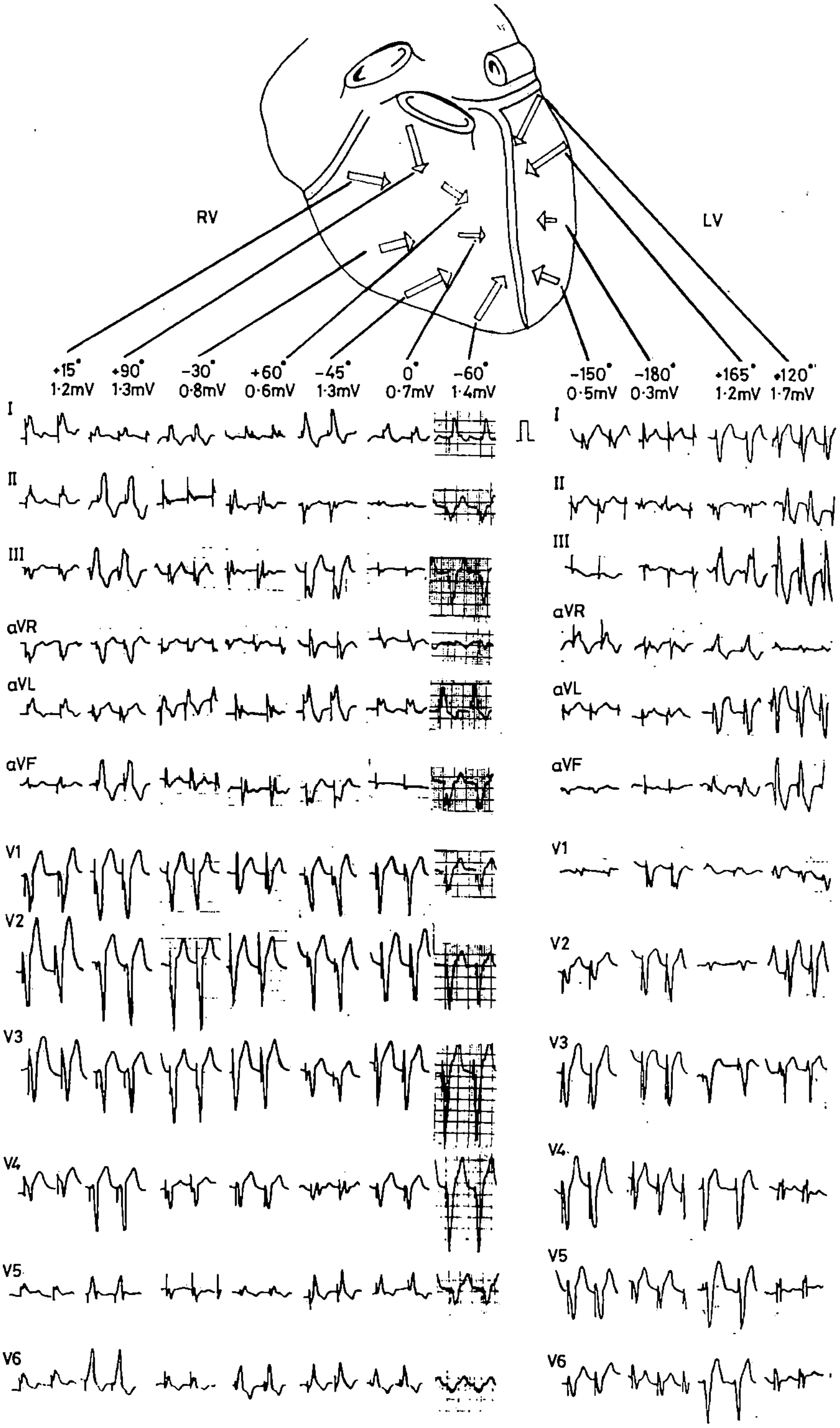

Fig. 4 *Twelve lead electrocardiographic appearances for the anterior ventricular sections recorded by pacing temporary epicardial wires postoperatively. Each electrocardiogram and the values above are taken from one patient, and are examples of the values recorded in that group in whom the same section was paced. The arrows summarise the limb lead QRS appearances as in Fig. 2.*

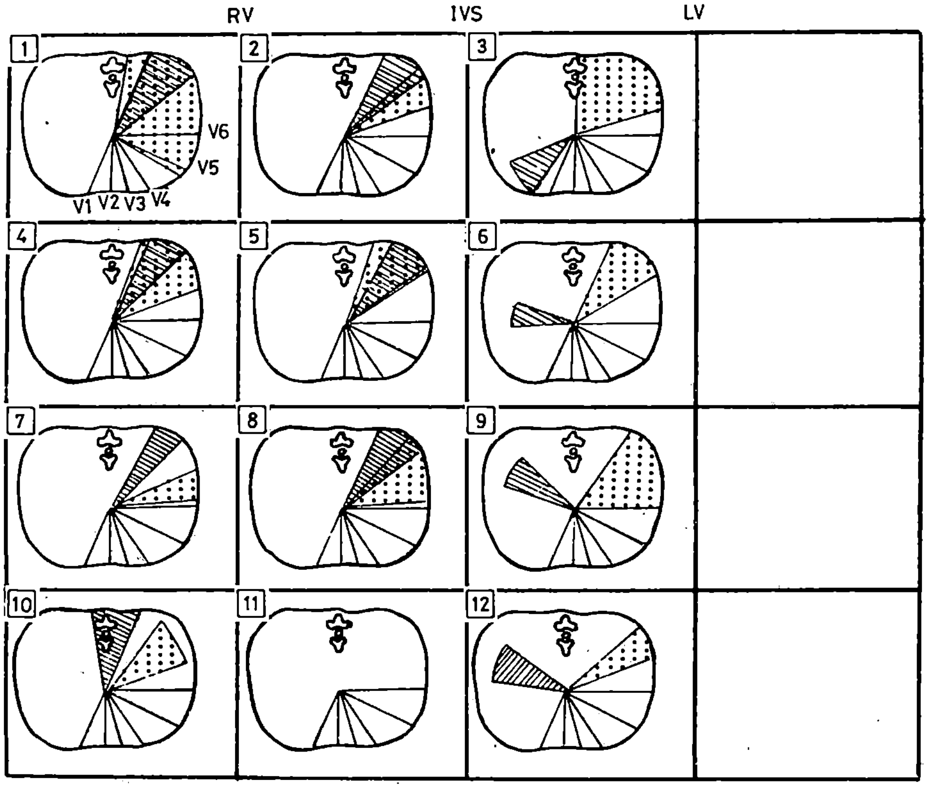

Fig. 5 *Diagram showing by means of arcs the range of horizontal lead axes encountered in patients with temporary epicardial wires inserted in the anterior sections. Stippled areas represent precordial lead axis during sinus rhythm; hatched areas represent precordial lead axis during pacing. The radius of the arcs represents the mean maximum amplitude of the precordial lead QRS complexes. RV, right ventricle; IVS, interventricular septum; LV, left ventricle.*

in a patient with previous anterior infarct (see adjacent section 20).

Bundle branch block—Right bundle branch block occurred infrequently. Only six patients had right bundle branch block on their resting electrocardiogram: five had temporary epicardial wires placed in the posterior right ventricle and one in the posterior left ventricle. It did not affect the limb lead or precordial lead axis or the duration of the paced ventricular complexes. Six patients had pre-existing left bundle branch block. Three had temporary epicardial wires positioned in the anterior right ventricle, one in the posterior right ventricle, and two in the left ventricle, one anteriorly, the other posteriorly. The paced electrocardiograms appeared uninfluenced by the presence of left bundle branch block on the resting electrocardiogram.

Left ventricular hypertrophy—Ten of 124 patients included in the second study had the voltage criteria of left ventricular hypertrophy on their resting electrocardograms. Five of these had epicardial wires inserted into the anterior right ventricle and three into the posterior right ventricle. Two patients had posterior left ventricular pacing wires. Left ventricular hypertrophy did not affect the limb lead or precordial lead QRS axes or the QRS duration of the paced complexes. The QRS amplitude of the paced complexes was, however, larger in those with left ventricular hypertrophy.

Discussion

Using pace mapping we have produced a working atlas of ventricular arrhythmias, an application of pace mapping that was envisaged in 1979.[11] The 12 lead electrocardiographic appearances from ventricular activation vary according to the site paced. Pacing the same site in different patients gives rise to similar electrocardiographic appearances. It is now possible not only to identify the ventricle of origin but also to localise ventricular arrhythmias to a region of that ventricle using the conventional 12 lead electrocar-

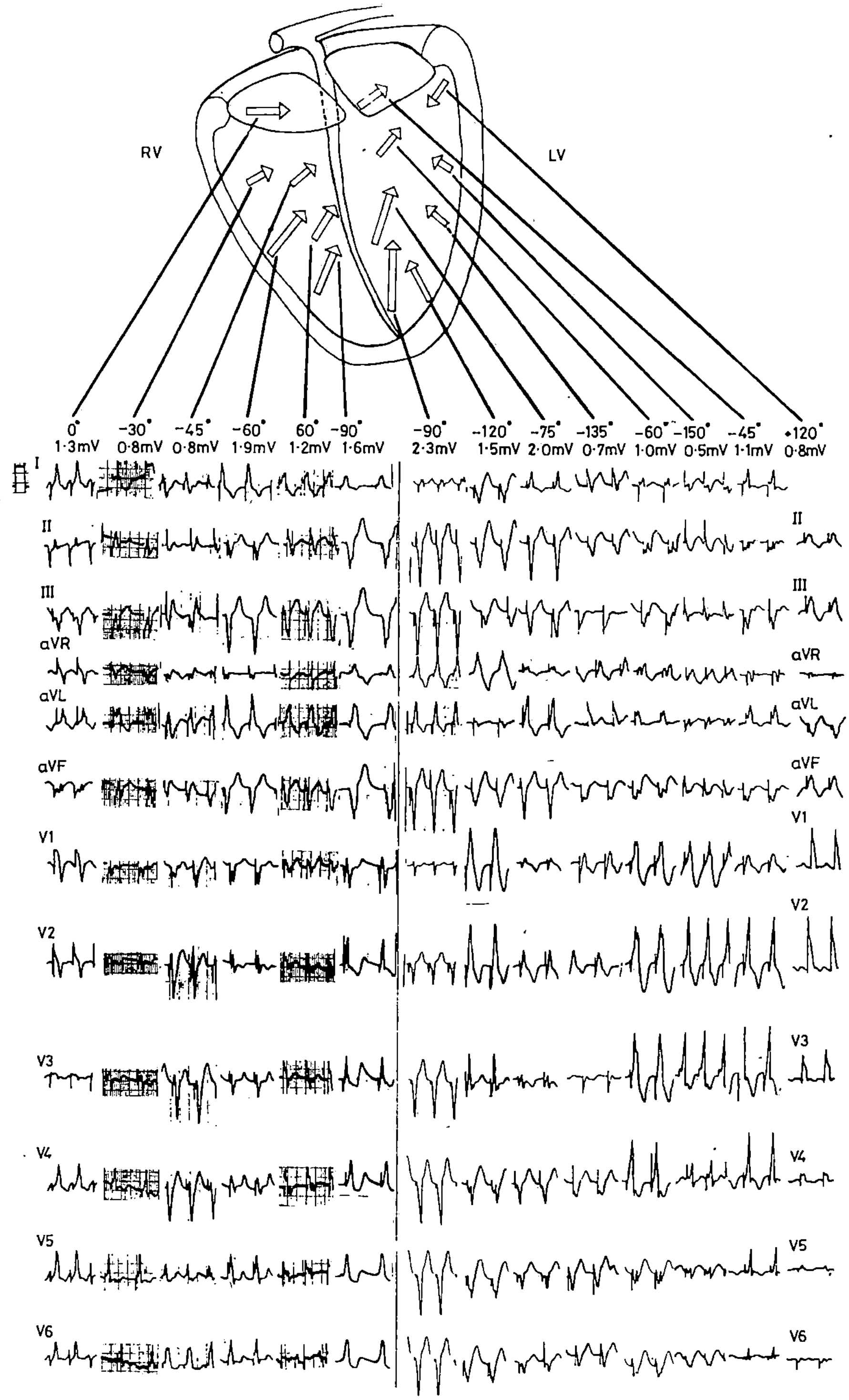

Fig. 6 *Electrocardiograms from individual patients in whom the posterior ventricular sections were paced representing the results obtained when that same section is paced in different patients. The paced tracing of section 19 has small initial R waves in V1–V4 and was taken from a patient with a previous anterior myocardial infarction (see text). RV, right ventricle; LV, left ventricle.*

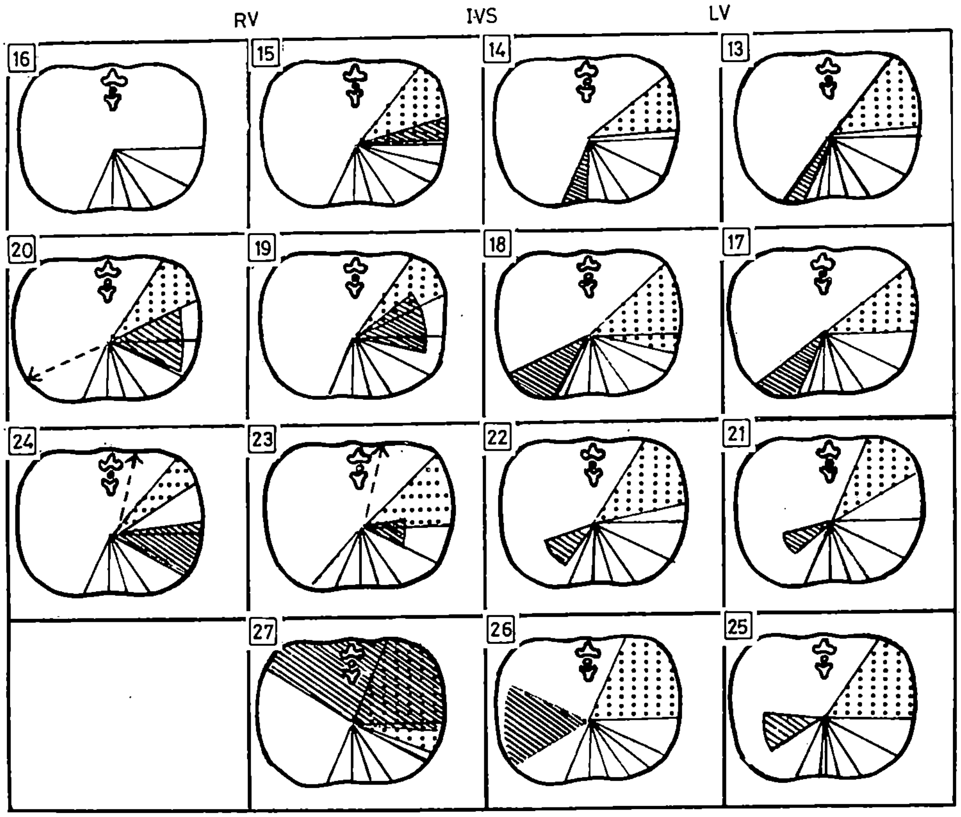

Fig. 7 *Diagrammatic summary of precordial lead axes obtained in patients with temporary epicardial wires inserted in the posterior ventricular sections. Stippled areas represent precordial lead axis during sinus rhythm; hatched areas represent precordial lead axis during pacing; broken arrow denotes patients with bundle branch block on the resting electrocardiogram. RV, right ventricle, LV, left ventricle, IVS, interventricular septum.*

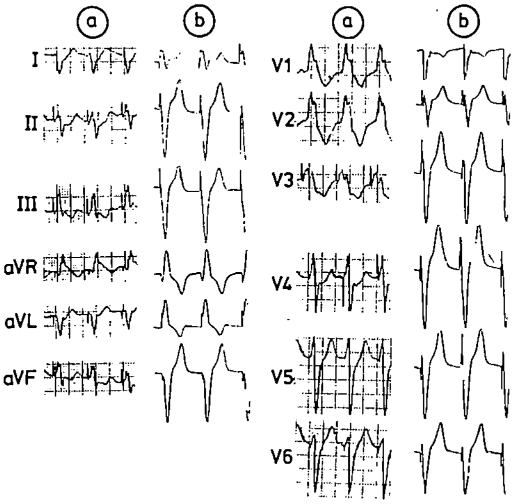

Fig. 8 *Electrocardiograms on pacing the (a) anterior and (b) posterior mitral valve papillary muscles recorded from individual patients but representative of the results obtained from the whole group of patients in whom the mitral valve papillary muscles were paced.*

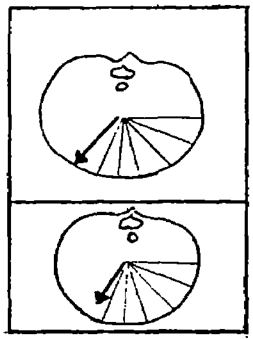

Fig. 9 *Diagram showing the precordial lead QRS axes produced on pacing the anterior papillary muscle (top) and posterior papillary muscle of the mitral valve.*

diogram. Since the mechanism[12] of a ventricular arrhythmia has no bearing on its final electrocardiographic appearances the atlas can be applied to the localisation of focal, triggered, and re-entry types.

The most important of the 12 electrocardiographic leads in identifying the segment from which the tachycardia arises in the long axis of the heart is lead II. This is shown in Figs. 2 and 4 by the transition of the main QRS deflection from positivity to negativity in this lead as the site of simulated ventricular tachycardia moves from the base to the apex of the heart respectively.

The electrocardiographic effects produced by a transition of simulated ventricular tachycardia loci across the ventricles from right to left are best seen in the precordial leads and also in lead I, in which the paced QRS deflection becomes more negative as the site of stimulation is moved from right to left. The transition of the paced QRS in lead I from positivity to negativity on stimulating the posterior ventricles does not occur at the anatomical landmark of the interventricular septum but is shifted somewhat towards the left ventricle. This confirms Abramson *et al's* findings.[7]

Our results show that ventricular arrhythmias with an inferior frontal plane QRS axis and a posterior leftward horizontal plane QRS axis originate from the anterobasal region of the right ventricle. Arrhythmias with a superior frontal plane QRS axis need careful scrutiny of their precordial lead appearances. Those with a posteroleftward horizontal plane QRS axis originate from the anterior and apical regions of the right ventricle and those with a leftward horizontal QRS axis from the posterior right ventricle. Attention to QRS duration further improves discrimination.

Certain pairs of right ventricular sections (4 and 7; 10/11 and 27; 19 and 20), however, produced paced electrocardiograms with very similar appearances. Therefore arrhythmias from these sites can be reliably resolved into only three and not six sections from their surface 12 lead electrocardiograms. In addition, the electrocardiogram from section 19 (Fig. 6) is very similar to that for section 7 (Fig. 4) and was obtained from a patient with previous anterior myocardial infarction. The resultant loss of R waves in the paced precordial lead complexes (V1–4) shifts the horizontal axis, in this example from section 19, into the same range as that obtained by pacing sections from the anterior ventricles.

Simulated arrhythmias from the base of the left ventricle anteriorly and laterally have an inferior frontal plane QRS axis and an anterorightward horizontal plane QRS axis. Left ventricular arrhythmias with a superior frontal plane QRS axis are readily distinguished by analysing their precordial leads; those with a posterorightward horizontal QRS axis originate from the anterior left ventricle and those with an anterorightward horizontal QRS axis from the posterior left ventricular sections. Arrhythmias from only two left ventricular sections (3 and 13) show appreciable overlap of their electrocardiographic appearances and are therefore not readily distinguished by the surface 12 lead electrocardiogram.

In this study we analysed the results of pacing small numbers of patients from a large number of ventricular sites in an attempt to give a detailed electrocardiographic atlas. Pacing more patients from fewer sites would have allowed better evaluation of the reproducibility of the electrocardiographic morphology and possibly the effects of underlying disease. Comparatively small changes in the site of pacing can, however, produce electrocardiographic changes, especially in the left ventricle. Therefore pacing fewer larger sections in the same patients would considerably diminish the electrocardiographic detail of the atlas.

Josephson *et al* reported the unusual presence of a left bundle branch block QRS morphology in the surface electrocardiogram during ventricular tachycardia that, according to the site of earliest recorded activa-

Table 3 *Results of electrocardiograms produced by pacing the mitral valve papillary muscles postoperatively*

Papillary muscle	*Frontal plane QRS axis*	*Limb lead QRS amplitude (mV)*	*Limb lead QRS duration (mV)*
Anterior	−165°	0·7	0·14
	−165°	1·4	0·12
	−180°	1·4	0·12
Mean	−170°	1·17	0·13
Posterior	− 90°	1·0	0·12
	− 90°	1·1	0·12
Mean	− 90°	1·05	0·12

tion, was arising from the left ventricle.[13] [14] Virtually all these patients, however, had left ventricular aneurysms associated with the arrhythmia. The development of a ventricular aneurysm may appreciably disrupt the spread of the depolarisation front and cause variable activation patterns in the same tachycardia. Great caution must, therefore, be exercised in interpreting the surface electrocardiograms of those patients with ventricular tachycardia and ventricular aneurysm. Further experience is needed with pace mapping studies in such cases. None of the patients included in our study had a left ventricular aneurysm.

Following our preliminary communication[11] Waxman and Josephson and Josephson *et al* also studied electrocardiographic patterns produced by pacing different sites on the left ventricular endocardium and compared them with operative findings.[15] [16] They studied 14 patients using percutaneous electrodes, but not all of the selected mapping sites were paced in each patient. Localisation of the pacing tip was judged by multiplane fluoroscopy with its inherent inaccuracies.

Our observations from epicardial pace mapping studies corroborate their findings during endocardial studies of large R waves in the precordial leads on pacing the posterior left ventricular sites and small R waves and deep S waves in leads V1–6 on pacing the anterior left ventricular sections. The same trend of predominantly superiorly directed limb lead QRS axes from apical and posterior left ventricular sites was also confirmed. Because it was impossible to pace all possible sites, particularly the endocardial surface and the septum, this atlas strictly refers to arrhythmias arising from the epicardial surface.

Our work and previous studies have shown that the site of origin of ventricular tachycardia may be inaccurately identified if attention is confined to the arrhythmia appearances in only a limited number of electrocardiographic leads.[14] The so called left or right bundle branch block classification[17] is insufficiently precise. The entire 12 lead electrocardiogram of a ventricular tachycardia should be scrutinised. Any factors that influence QRS axes (for example, previous myocardial infarction) should be taken into account.

This atlas of ventricular arrhythmias has clinical implications since it allows the site of the ventricular tachycardia to be compared with that of the underlying cardiac disease. For example, ventricular tachycardia complicating the mitral valve prolapse syndrome has been shown to arise from the mitral papillary muscles.[18] More recently the relation between sites of ischaemia (localised on an electrocardiogram) and of ventricular arrhythmias has been studied clinically.[19–22] Our atlas may be used to localise ventricular arrhythmias to specific coronary artery territories in those with ischaemia.[23]

Another application of the electrocardiographic atlas is to the preoperative localisation of a refractory ventricular tachycardia requiring ablation either surgically or by high energy impulses.[24] [25] The feasibility of the procedure in terms of accessibility of the tachycardia can be considered and the duration of the peroperative mapping procedure reduced by a prior awareness of the area of interest. By means of a standard simple investigation the 12 lead electrocardiographic ventricular arrhythmias can now be more accurately localised.

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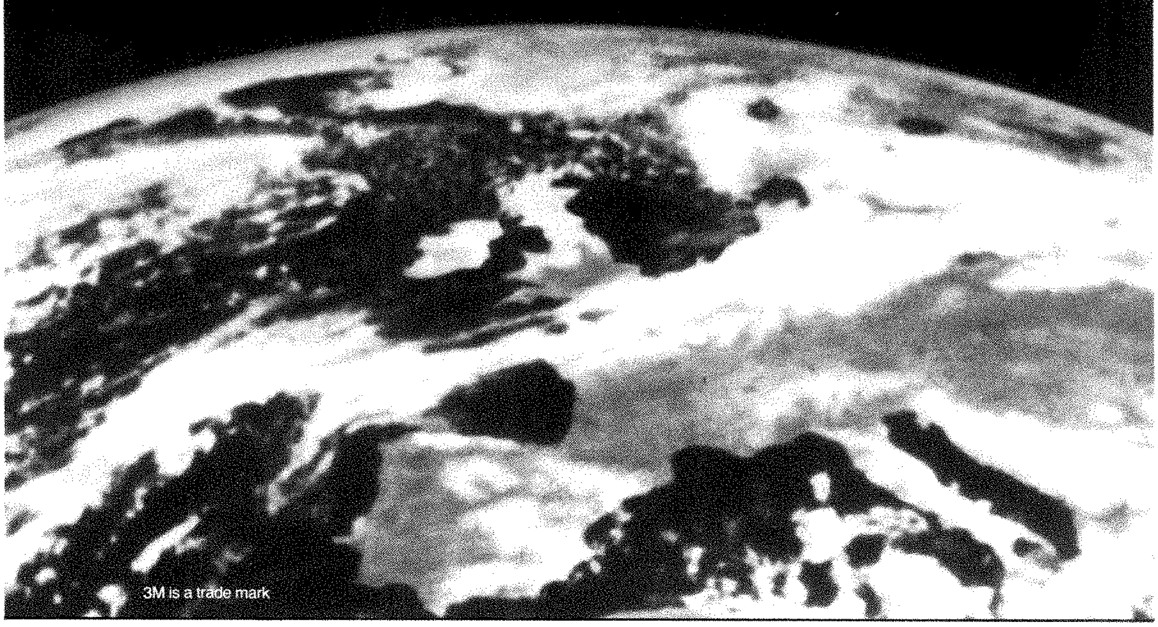

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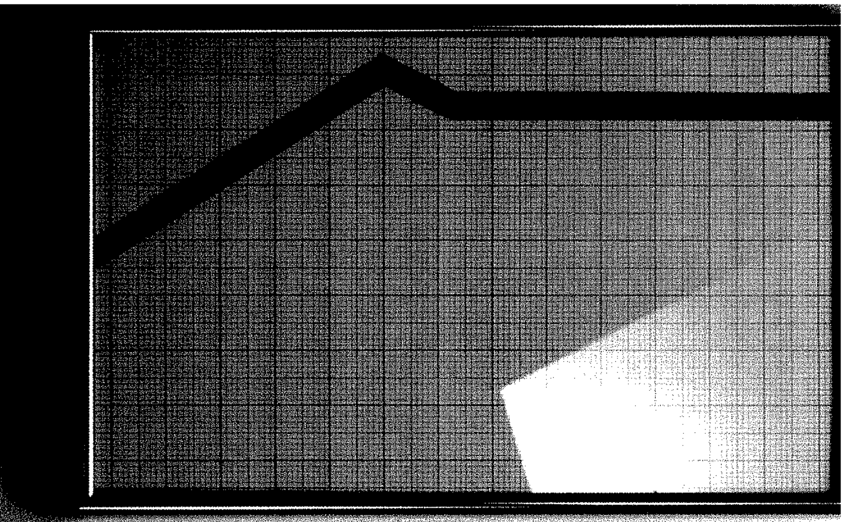

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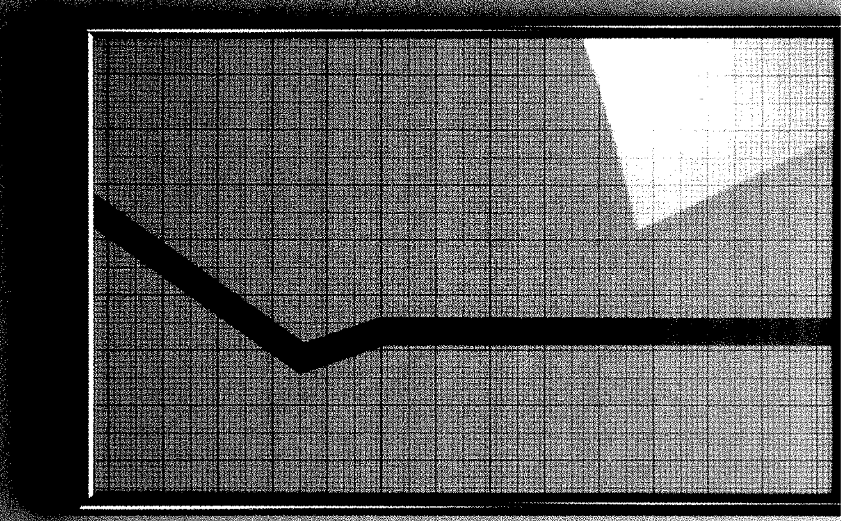

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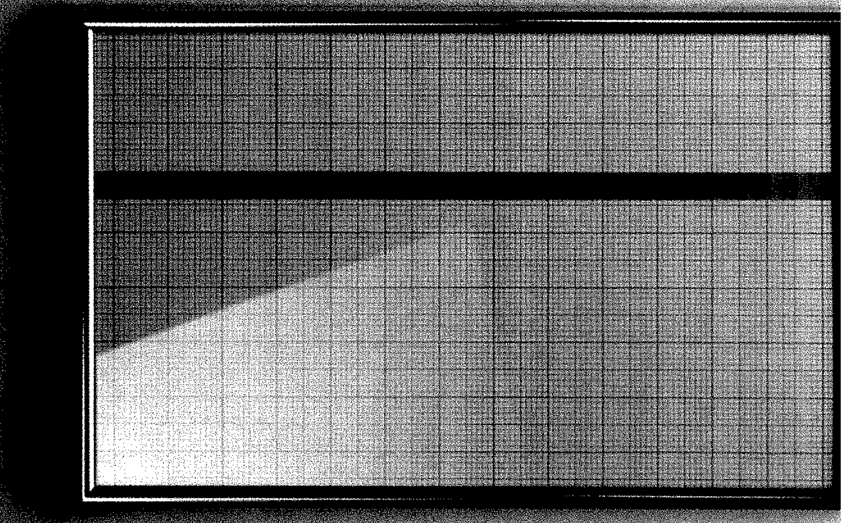

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DOSAGE

Essential hypertension. The usual maintenance dosage is 20 mg once daily. Treatment may be initiated with 10 mg or 20 mg once daily dependent on degree of hypertension. For mild hypertension, recommended initial dosage is 10 mg once daily. For all other grades an initial dosage of 20 mg once daily recommended.

Renovascular hypertension. Initial dose is 10 mg a day, adjusted as necessary. Most patients should respond to 20 mg daily.

Congestive heart failure. Can be used as adjunctive therapy with diuretics and, where appropriate, digitalis. Initial daily dose 10 mg as a single or divided dose.

MODE OF ACTION

Following oral administration. 'Innovace' is rapidly absorbed and hydrolysed to enalaprilat, a highly specific, long-acting, non-sulphydryl angiotensin converting enzyme inhibitor.

CONTRA-INDICATIONS

Pregnancy: assessment for possible pregnancy required if menstrual period is missed.
Hypersensitivity.

PRECAUTIONS

Symptomatic hypotension rarely after initial dose. More likely following volume depletion caused by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. Blood pressure may drop in some patients with congestive heart failure who have normal or low blood pressure.

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of 'Innovace' and their renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Some hypertensive patients, with no apparent pre-existing renal disease, have developed minor and usually transient increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required.

Renovascular hypertension: 'Innovace' can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 'Innovace' is dialysable.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

DRUG INTERACTIONS

Increased antihypertensive effect when combined with methyldopa, ß-blockers, and diuretics. Add ganglionic- or adrenergic-blocking drugs with caution. Plasma potassium usually remains within normal limits. If 'Innovace' is given with a diuretic, diuretic-induced hypokalaemia may be ameliorated. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics should be given with caution, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. Lithium levels may be increased.

SIDE EFFECTS

Generally well tolerated. Most side effects mild and transient, and have not required discontinuation of therapy. Most frequently: dizziness, headache, fatigue, asthenia. Others include hypotension, orthostatic hypotension, nausea, diarrhoea, muscle cramps, rash, cough, dysgeusia, and angioneurotic oedema. With minor and transient rises in blood urea or creatinine, dosage reduction and discontinuation of 'Innovace' and/or the diuretic may be required.

BASIC NHS COST

Tablets 20 mg: calendar packs of 28 tablets, £13.10; bottles of 50 tablets, £23.40. Tablets 10 mg: calendar packs of 28 tablets, £10.40; bottles of 50 tablets, £18.57. Tablets 5 mg: bottles of 50 tablets, £12.30.

PRODUCT LICENCE NUMBERS

Tablets, 5 mg, 0025/0194, Tablets, 10 mg, 0025/0195, Tablets, 20 mg, 0025/0196.

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MERCK
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Issued February 1985

TM denotes trademark

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Haemodynamic and neurohumoral response to exercise in patients with congestive heart failure treated with captopril

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SUMMARY The contribution of the renin-angiotensin system to the cardiovascular response to exercise was studied in 12 patients with congestive heart failure. The haemodynamic effects of captopril were measured at rest and during supine bicycle exercise. After captopril administration, resting systemic vascular resistance fell by 26·6% and mean blood pressure by 16·7% and cardiac index increased by 19·7%. During exercise, captopril decreased systemic vascular resistance by 25·6% and mean blood pressure by 8·2% and increased cardiac index by 24·4%. Pulmonary wedge pressure fell by 25% at rest but was not altered by captopril during exercise. Pretreatment plasma renin activity increased from 13·4(16·0) ng/ml/hr (10·3(12·3) mmol/l/hr) at rest to 20·0(27·8) ng/ml/hr (15·4(21·4) mmol/l/hr) during exercise. Pretreatment plasma noradrenaline concentration increased from 659(433) pg/ml (39(25·6) nmol/l) at rest to 2622(1486) pg/ml during exercise (155(88) nmol/l). Captopril favourably alters systemic vascular resistance and cardiac index during exercise in patients with congestive heart failure. This may reflect inhibition of the increased activity of the renin-angiotensin system during exercise in these patients and a subsequent reduction in systemic vasoconstriction.

The renin-angiotensin system contributes to systemic vasoconstriction in patients with congestive heart failure. After the administration of saralasin (an angiotensin II antagonist) and of teprotide, captopril, and enalapril (angiotensin-converting enzyme inhibitors) resting cardiac function improves as a consequence of systemic vasodilatation.[1–10] A beneficial haemodynamic response during exercise also occurs after captopril administration. This includes an increase in cardiac output and stroke volume and a fall in systemic vascular resistance.[11 12] The clinical efficacy of captopril has been shown in placebo controlled trials.[12 13]

In resting patients the vasodilatation that accompanies converting enzyme inhibition correlates with the pretreatment resting plasma renin activity.[2 7 8] While plasma renin activity also increases during exercise in normal subjects, it is not established that plasma renin activity increases in patients with heart failure during exercise.[14 15] Activation of the renin-angiotensin system during exercise would further contribute to vasoconstriction and as a result limit the increase in cardiac output. Captopril may, therefore, inhibit angiotensin mediated vasoconstriction during exercise and thus improve cardiac function.

Some investigators have reported a fall in plasma noradrenaline concentration after converting enzyme inhibition, though this has not been confirmed by others.[3 6] During exercise, plasma noradrenaline increases in normal subjects and in patients with congestive heart failure.[14–17] A decrease in sympathetic nervous system activity may contribute to captopril mediated vasodilatation.

This study was therefore designed to assess the haemodynamic and neurohumoral response to captopril during exercise in patients with congestive heart failure. Plasma renin activity and noradrenaline concentrations were assessed at rest and during exercise

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to determine whether haemodynamic changes seen during exercise after converting enzyme inhibition can be explained by inhibition of the renin-angiotensin or sympathetic nervous systems.

Patients and methods

STUDY POPULATION

Twelve patients with symptoms and signs of severe congestive heart failure participated in the study. The group included 11 men and one woman (mean age 59(11) (range 37–74) years). The cause of congestive heart failure was coronary artery disease in six patients as documented by previous myocardial infarction or coronary angiography or both and hypertension in two. Four patients had a primary cardiomyopathy of unknown aetiology. Patients having sustained a myocardial infarction within three months or those with primary valvar pathology were excluded. The mean duration of heart failure was 5·2(3·5) years (range one month to seven years). Eight of the patients were categorised as being in New York Heart Association class III and four as being in class IV. All had been receiving digitalis and diuretic drugs. The mean radionuclide ejection fraction was 23·7(11·6)%. The protocol of the study had the approval of the Institutional Review Board for Human Research, and each patient gave informed consent.

Patients were admitted to hospital and maintained on a diet containing 86 mmol sodium daily for at least three days before the study. All vasodilators were withdrawn at least 48 hours before the investigation. Digitalis, diuretics, and all medications other than clinically necessary antiarrhythmic agents were withheld on the day of the haemodynamic study.

CENTRAL HAEMODYNAMIC ASSESSMENT

On the evening before the study, patients underwent right heart catheterisation with a Swan-Ganz catheter (Edwards Laboratories) and radial artery cannulation. Pressures were measured using a Hewlett-Packard model 1280 strain gauge transducer and recorded on a direct-writing Hewlett-Packard multigraph. Mean pressures were obtained by electronic integration. Zero reference was chosen at a level 5 cm vertically beneath the sternal angle. Heart rate was determined from the simultaneous electrocardiographic signal. Cardiac output was determined by the Fick method as detailed below. Thus measurements were obtained for systolic, diastolic, and mean blood pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and right atrial pressure. Hemodynamic indices and systemic resistance were calculated from pressure and output values according to standard formulas.[18]

RESPIRATORY GAS ANALYSIS AND DETERMINATION OF CARDIAC OUTPUT

A Beckman metabolic cart comprising a volume transducer, a Beckman OM-11 oxygen analyser, and a Beckman UB-2 carbon dioxide analyser was used to determine minute volume oxygen consumption ($\dot{V}O_2$), and minute volume carbon dioxide production ($\dot{V}CO_2$). Oxygen and carbon dioxide concentrations in expired air were delivered via a mouthpiece with a low resistance three way valve to a mixing chamber, volume transducer, and gas analyser. The gas analyser was calibrated with 4% carbon dioxide and 16% oxygen calibration gas. A model 1810 Monroe programmable calculator was used to calculate $\dot{V}O_2$ and $\dot{V}CO_2$. Blood was collected for arterial and mixed venous oxygen content. Blood for oxygen content was analysed on a Lex-O_2-Con oxygen analyser (Lexington Instruments). Cardiac output was calculated as the ratio of the $\dot{V}O_2$ to the arteriovenous oxygen content difference.

PLASMA RENIN ACTIVITY AND PLASMA NORADRENALINE CONCENTRATION MEASUREMENTS

Samples of mixed venous blood for measurement of plasma renin activity and noradrenaline concentration were collected while the patients were resting supine and at peak exercise, before and after captopril administration. The collection of blood coincided with the haemodynamic measurements. Blood specimens for plasma renin activity and noradrenaline concentration were immediately placed on ice and centrifuged at 4°C. Plasma renin activity was determined by a radioimmunoassay for angiotensin I generation and plasma noradrenaline concentration by a radioenzymatic assay.[19 20]

STUDY PROTOCOL

Patients were studied after fasting overnight without premedication. Haemodynamic measurements were made while patients were lying supine. Systemic haemodynamic data were collected until three successive determinations 10 minutes apart showed homeostasis. Simultaneous respiratory gas analysis also assured a stable resting state. Patients then began exercise on a Quinton supine bicycle ergometer at a workload of 33 W (200 kpm), pedalling at 40 to 50 rev/min. The duration of this stage was three minutes. The workload was increased by 8 W (50 kpm) every three minutes. Haemodynamic measurements, collection of arterial and mixed venous blood for oxygen content, and respiratory gas analysis were performed during the last minute of each stage. Exercise was terminated when the patient was unable to continue because of dyspnoea or fatigue. Haemodynamic measurements and respiratory gas analysis were

Table *Effect of captopril on systemic haemodynamics and oxygen consumption at rest and during exercise. Values are mean (SD)*

	Rest			*Exercise*		
	Control	*Captopril*	*p value **	*Control*	*Captopril*	*p value **
$\dot{V}O_2$ (ml/min)	239 (45)	268 (130)	NS	689 (94)	678 (94)	NS
Systemic vascular resistance (dyn s cm^{-5})	2138 (802)	1569 (614)	<0·01	1719 (766)	1275 (487)	<0·05
Blood pressure (mm Hg)	99 (20)	82 (17)	<0·01	113 (24)	104 (21)	<0·01
Cardiac index (l/min per m^2)	2·1 (0·8)	2·6 (0·9)	<0·05	3·5 (1·7)	4·4 (2·4)	<0·05
Stroke volume index (ml/m^2)	26 (11)	31 (14)	<0·05	29 (15)	39 (16)	<0·05
Heart rate (beats/min)	88 (18)	85 (18)	NS	122 (20)	114 (17)	NS
Pulmonary capillary wedge pressure (mm Hg)	28 (11)	21 (9)	<0·05	39 (10)	36 (10)	NS

*Significant differences between values obtained during the control period and those obtained after captopril administration.

obtained during the minute before exercise termination. A plateau of $\dot{V}O_2$ and a disproportionate rise in $\dot{V}CO_2$ signalled the onset of anaerobic metabolism and maximal exercise capacity.

Patients were allowed to rest for at least four hours. After baseline conditions were re-established and homeostasis again assured, captopril 25 mg was given orally. Resting haemodynamic measurements were repeated 30 and 45 minutes later. Incremental supine bicycle exercise was then repeated to maximal tolerance as described above, with haemodynamic measurements, blood collection, and respiratory gas analysis being obtained during the last minute of each stage. Each patient again exercised to fatigue as verified by a plateau in $\dot{V}O_2$ and a disproportionate increase in $\dot{V}CO_2$.

STATISTICAL ANALYSIS

Values are expressed as mean (SD). Data at rest and during exercise and before and after captopril were analysed by the paired *t* test or the Wilcoxon rank sum test. Measurements obtained at rest and during maximal exercise before treatment were compared with those obtained at rest and during the comparable exercise stage after treatment. Statistical significance is defined as $p<0{\cdot}05$.

Results

RESTING HAEMODYNAMIC RESPONSE TO CAPTOPRIL (TABLE, FIG. 1)

There was no significant difference in any of the resting haemodynamic variables obtained before exercise on the morning of the investigation and before administration of captopril several hours after the completion of exercise. Thus a resting baseline was re-established before captopril administration. Captopril decreased the mean blood pressure by 16·7% ($p<0{\cdot}01$) and the systemic vascular resistance by 26·6% ($p<0{\cdot}01$), while the cardiac index increased by 19·7% ($p<0{\cdot}05$). Since there was no significant change in heart rate, the increment in cardiac index was secondary to a 16·7% increase in stroke volume index ($p<0{\cdot}05$). Captopril reduced the pulmonary capillary wedge pressure by 24·6% ($p<0{\cdot}05$).

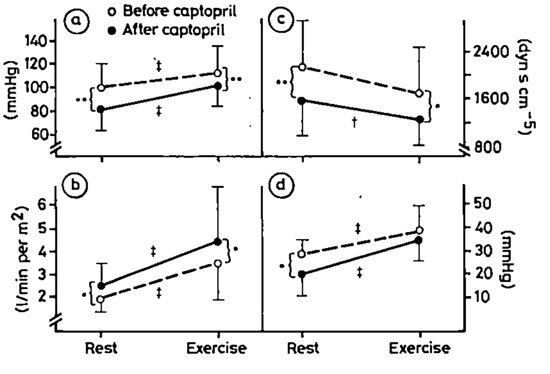

Fig. 1 *Effect of captopril on (a) blood pressure, (b) cardiac index, (c) systemic vascular resistance, and (d) pulmonary capillary wedge pressure at rest and during exercise. Values are mean (SD).* * $p<0{\cdot}05$ *precaptopril* vs *postcaptopril;* ** $p<0{\cdot}01$ *precaptopril* vs *postcaptopril;* † $p<0{\cdot}05$ *rest* vs *exercise;* ‡ $p<0{\cdot}01$ *rest* vs *exercise.*

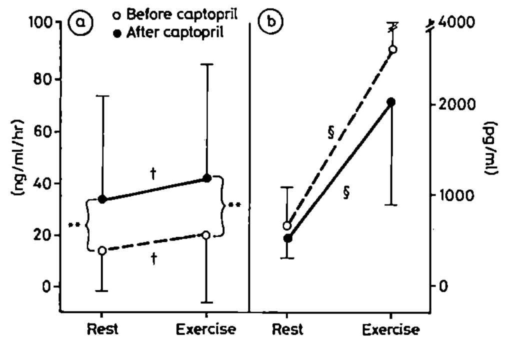

Fig. 2 *Effect of captopril on (a) plasma renin activity and (b) plasma noradrenaline concentration at rest and during exercise. Values are mean (SD).* ** $p<0{\cdot}01$ *precaptopril* vs *postcaptopril;* † $p<0{\cdot}01$ *rest* vs *exercise;* § $p<0{\cdot}001$ *rest* vs *exercise.*

Conversion: traditional to SI units—renin: 1 ng/ml ≈ 0·77 mmol/l; noradrenaline 1 pg/ml ≈ 0·059 nmol/l.

EFFECT OF CAPTOPRIL ON EXERCISE HAEMODYNAMICS (TABLE, FIG. 1)

During maximal exercise, captopril reduced the mean blood pressure by 8·2% ($p<0·01$) and systemic vascular resistance by 25·6% ($p<0·05$). The cardiac index increased by 24·4% ($p<0·05$) and the stroke volume index by 32·9% ($p<0·05$). The heart rate during exercise did not differ after captopril compared with pretreatment values. Captopril did not decrease the pulmonary capillary wedge pressure during exercise. There were no significant changes in exercise duration from a pretreatment time of 5·1(1·9) minutes or in maximal oxygen consumption from a pretreatment value of 689(94) ml/min after captopril. The respiratory quotient, or ratio of $\dot{V}CO_2$ to $\dot{V}O_2$, was 1·0(0·1) at maximal exercise before treatment and 1·1(0·1) after captopril (NS).

PLASMA RENIN ACTIVITY AND NORADRENALINE CONCENTRATION (FIG. 2)

The resting plasma renin activity was 13·4(16·0) ng/ml/hr (10·3(12·3) mmol/l/hr). During exercise, before captopril, the plasma renin activity increased to 20·0(27·8) ng/ml/hr (15·4(21·4) mmol/l/hr) ($p<0·01$). After captopril, the resting plasma renin activity increased further to 32·8(39·9) ng/ml/hr (25·2(30·7) mmol/l/hr) ($p<0·01$) and during exercise the value was 44·5(46·1) ng/ml/hr (34·2(35·5) mmol/l/hr) ($p<0·01$ *vs* control).

The pretreatment resting plasma noradrenaline concentration was 659(433) pg/ml (39(26) nmol/l). During supine bicycle exercise, before captopril, values increased to 2622(1486) pg/ml (155(88) nmol/l) ($p<0·001$). After captopril, neither the resting nor exercise noradrenaline concentration changed significantly.

Discussion

The improvement in resting cardiac function seen after the administration of captopril in this study is similar to that previously reported.[4–8] Cardiac output and stroke volume increased as a consequence of the systemic vasodilatory effects of angiotensin converting enzyme inhibition. The fall in pulmonary capillary wedge pressure may be secondary to venodilatation or improved ventricular compliance. Mild and transient increases in limb venous volume have been found with captopril in patients with congestive heart failure and may account, in part, for the reduction in left ventricular filling pressure.[6]

Indices of cardiac function improved during exercise after captopril administration. Cardiac output was greater and systemic vascular resistance lower than pretreatment values. Since captopril did not alter the heart rate the increase in cardiac output during exercise is attributed solely to an increase in stroke volume. Captopril has no known positive inotropic properties and therefore the increase in stroke volume must be a consequence of systemic vasodilatation.

In this study resting plasma renin activity and plasma noradrenaline concentration were higher than values usually obtained in normal subjects in our laboratory.[21] Both plasma renin activity and plasma noradrenaline concentration increased during exercise before captopril. The increase in plasma noradrenaline concentration during exercise in patients with heart failure has been reported by others.[16 17] To our knowledge, an increase in plasma renin activity during exercise has not been previously reported in patients with heart failure. It is, however, known to occur in normal subjects.[14 15] Plasma renin activity increased after captopril at rest and during exercise. This increase reflects a loss of negative feedback inhibition consistent with a decrease in angiotensin II concentrations. The vasoactive effects of captopril, however, may also be mediated via the kallikrein-kinin and prostaglandin systems; therefore, modulating effects of these hormonal systems cannot be excluded.[22 23] After captopril, plasma noradrenaline concentration did not fall either at rest or during exercise. Thus a decrease in sympathetic nervous system activity cannot explain the observed vasodilatation.

During exercise, when autoregulatory phenomenon as well as activation of the renin-angiotensin system and sympathetic nervous system occur, it is not known whether the increased blood flow associated with captopril administration is distributed to exercising muscle or non-exercising tissue. Exogenous administration of angiotensin II produces varying degrees of vasoconstriction depending on the specific regional circulation.[24 25] Pharmacological doses of angiotensin II result in pronounced vasoconstriction in the limbs of normal subjects.[26 27] In experimental studies using sodium depleted dogs, converting enzyme inhibition significantly improves adrenal, cerebral, coronary, and renal blood flow but causes only a modest increase in skin blood flow and no improvement in muscle blood flow.[28] In patients with heart failure studied at rest, captopril does not have a uniform effect on each regional circulation.[6 29 30] The increase in renal blood flow is disproportionate to the negligible changes that occur in limb, splanchnic, and coronary blood flow.

Since the renin-angiotensin system is stimulated during effort in patients with heart failure, it is possible that the higher concentrations of angiotensin II will have a greater influence on limb vascular resistance during exercise than at rest. Kugler and colleagues, however, have suggested that blood flow to exercising muscle was not increased by angiotensin blockade since femoral vein oxygen content measured during bicycle exercise did not change after captopril.[11] In that study, however, limb blood flow was not actually measured.

If blood flow to exercising muscle is influenced by the renin-angiotensin system exercise capacity after the administration of captopril might be expected to improve. Other investigators have assessed the exercise response to captopril and have not found an improvement in exercise capacity after short term administration.[12] An acute increase in exercise capacity and maximal oxygen consumption has been reported in patients with heart failure after enalapril treatment.[31] Studies of limb blood flow during exercise are required during angiotensin II inhibition for further elucidation.

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Relation between mitral valve closure and early systolic function of the left ventricle

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SUMMARY In order to investigate relations between mitral valve closure and mechanical events at the onset of left ventricular systole, simultaneous M mode echocardiograms and phonocardiograms were recorded with the apexcardiogram and its first differential (dA/dt) in 25 normal subjects and 88 patients with heart disease. The timing of mitral and aortic valve closure and the onset and peak rate of rise of the apexcardiogram with respect to the Q wave of the electrocardiogram were measured. There was considerable variation in the intervals from Q to mitral valve closure (Q-MVC) and from Q to peak dA/dt and in the isovolumic contraction time between normal subjects. There was no consistent abnormality of these intervals in patients with coronary artery or valvar disease, and no relation between the interval from Q to mitral valve closure and end diastolic pressure. When the timing of the first heart sound and peak dA/dt were considered together, however, clear abnormalities became apparent. In normal subjects, the intervals Q-MVC and Q to peak dA/dt were significantly correlated. In coronary artery disease, the expected relation between Q-MVC and Q to peak dA/dt was found only when end diastolic pressure was normal and was lost when end diastolic pressure was raised. Mitral stenosis was associated with delayed mitral closure in a few cases only, but in chronic aortic regurgitation closure was consistently early with respect to the apexcardiogram. In patients with atrial fibrillation and a normal mitral valve the timing of mitral valve closure with respect to the apexcardiogram was normal, which is inconsistent with an atrial contribution to the timing of mitral valve closure. Thus when considered in isolation the timing of mitral valve closure and the duration of isovolumic contraction time gave little information about cardiac function. Nevertheless, a predictable relation exists between mitral valve closure and the onset of left ventricular mechanical systole in normal subjects, which can be used to identify characteristic alterations in patients with heart disease.

Mitral valve closure is an important landmark in the cardiac cycle. It signals the onset of the period of isovolumic contraction and is a major determinant of the timing and intensity of the first heart sound. The exact mechanism by which it occurs has long been an object of study, yet there is still no agreement on the relative importance of atrial and ventricular contraction in leading to closure[1] or on the ways in which these factors may be modified in disease. The purpose of the present study was to investigate the interrelations between the timing of mitral valve closure as shown by M mode echocardiography, the onset of the mechanical events of left ventricular systole as reflected in the apexcardiogram, and the duration of isovolumic contraction in normal subjects and patients with heart disease.

Patients and methods

STUDY GROUPS

Twenty five normal subjects and 88 patients with heart disease were studied. The normal subjects were aged between 23 and 58 (median 39) years with no history or clinical evidence of heart disease and no significant abnormality on echocardiography. Of the 88 patients, 44 (aged 21–76 years) were found at cardiac catheterisation to have coronary artery disease.

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Valve disease was present in 38 patients, including 10 with mitral stenosis (eight in atrial fibrillation), two with mixed mitral valve disease (both in atrial fibrillation), seven with mitral Starr-Edwards prosthesis (all in atrial fibrillation), eight with aortic stenosis, and 13 with chronic aortic regurgitation or mixed aortic valve disease, all in sinus rhythm. In order to study the effects of atrial systole, six further patients with atrial fibrillation but with no other demonstrable cardiac abnormality were also studied.

ECHOCARDIOGRAPHY

M mode echocardiograms were recorded to display first the mitral valve (Fig. 1) and then the aortic valve cusps, together with a simultaneous electrocardiogram, apexcardiogram and its first derivative, and phonocardiogram on each. A Cambridge Instruments recorder was used, operating at a paper speed of 100 mm/s. The apexcardiogram transducer had a time constant of 4 s, and the differentiating circuit was fitted with a low pass filter with a 3 dB cut off of 300 Hz to reduce noise. All patients were examined in the left semilateral position during quiet respiration. In those patients in whom cardiac catheterisation was performed, left ventricular end diastolic pressure (pre-a) was noted. Invasive and non-invasive investigations were performed within 24 hours of one another, and in no patient was there any perceptible change in clinical state during this interval.

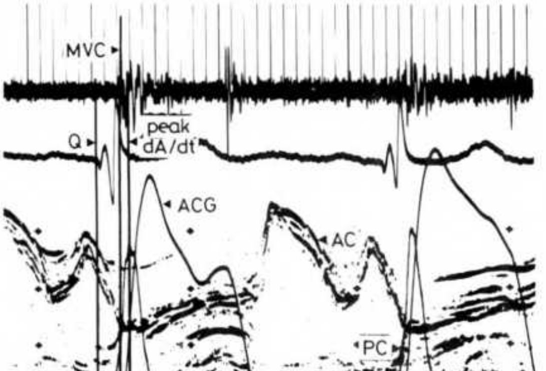

Fig. 1 *Simultaneous M mode echocardiogram and apexcardiogram (ACG), indicating the measurements made. Q, onset of the Q wave of the electrocardiogram; MVC, mitral valve closure; peak dA/dt, peak of the first derivative of the apexcardiogram; AC, anterior (and PC posterior) cusps of the mitral valve.*

MEASUREMENTS

The onset of the Q wave of standard lead II was taken as the reference point for all measurements. If a Q wave was not present the onset of the R wave was taken as representing the earliest deflection of the QRS complex. Mitral valve closure was taken as the time of complete coaptation of the leaflets, using the minimum gain of the echocardiograph with which this could be demonstrated. Records showing multiple echoes, or approximation of cusp echoes rather than complete closure, were rejected as unsuitable for measurement. Aortic valve opening was taken as the onset rather than the completion of the opening movement. It was possible to obtain satisfactory measurements of the time of mitral valve closure in patients with mitral valve disease, but aortic valve opening could not usually be assessed in those with aortic valve disease, particularly when the valve was calcified. For the apexcardiogram, the onset of the upstroke (C point) was taken as that of the rapid rise after the "a" wave, although in some cases, particularly when the "a" wave was increased in amplitude, it was difficult to define. The timing of peak rate of rise was usually clear, but in a small number of cases, particularly when mitral closure was delayed with respect to the Q wave of the electrocardiogram, its pattern was bifid or plateau shaped; in these circumstances, the timing of the first peak was used for measurement.

The following time intervals were measured: (*a*) Q to C point of apexcardiogram (Q-C); (*b*) Q to peak rate of rise of apexcardiogram (Q to peak dA/dt); (*c*) Q to mitral valve closure (Q-MVC); and (*d*) the interval from mitral closure to aortic opening, which was referred to as isovolumic contraction time, although in some cases small volume changes might have occurred owing to some degree of mitral regurgitation. In patients with sinus rhythm mean values for these intervals were obtained from 7–10 cycles, and in patients with atrial fibrillation individual results from 20–80 complexes were used. All time intervals were expressed to the nearest 5 ms.

The possibility that a significant delay occurred between echocardiographic, phonocardiographic, and apexcardiographic measurements had previously been checked in vitro. In order to test the system in vivo, however, simultaneous measurements were made in seven patients with mitral Starr-Edwards prostheses. It was assumed that the closing click of the prosthesis was due to the ball impinging on the cage at the start of ventricular systole. In all cases, there was no more than a 5 ms difference between the cessation of the posterior motion of the ball, demonstrated by echocardiography, the onset of the first high frequency vibration of the click, and the onset of a characteristic deflection on the first differential of the apexcardiogram corresponding to the click.

STATISTICAL METHODS

Results were analysed using Student's *t* test, Fisher's exact probability test, or non-parametric tests when variables were not normally distributed. The 95% confidence limits about mean values were taken as two standard deviations. Correlation coefficients were calculated by the method of least squares.

Results

NORMAL SUBJECTS

The mean (SD) interval from the onset of the QRS complex to mitral valve closure was 60 (10 ms). The onset of the upstroke of the apexcardiogram occurred 25 (10) ms and the peak rate of rise 85 (10) ms after the Q wave of the electrocardiogram. There was thus appreciable scatter between these variables in different normal individuals. There was, however, a significant correlation between the intervals Q to mitral valve closure and Q to peak rate of rise (Fig. 2). The regression equation was: (Q to peak dA/dt)=0·66(Q-MVC)+45 ms. The correlation coefficient was 0·79 and the standard error of the estimate 5 ms. The standard error of the slope was 0·11 and of the intercept 6 ms. The correlation between Q-MVC and Q-C was very much less close, the correlation coefficient being 0·39. In retrospect, this seemed to be due to difficulty in identifying the onset of the upstroke even in the presence of a normal "a" wave. The interval Q to aortic valve opening, equivalent to pre-ejection period, had a mean value of 90 (10) ms. Isovolumic contraction time showed considerable scatter: the mean value was 30 (10) ms with values ranging from 15 to 55 ms.

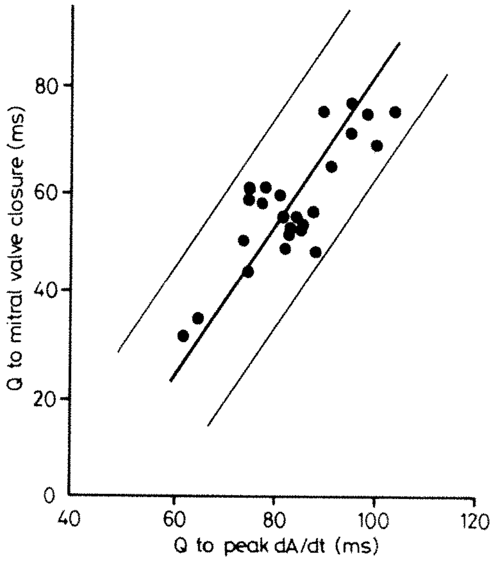

Fig. 2 *Relation between the intervals Q to mitral valve closure and Q to peak dA/dt in normal subjects. The regression line and bounds set at two standard deviations (95% confidence limits) are shown.*

PATIENTS WITH HEART DISEASE

Timing of mitral closure—The time interval Q-MVC was within normal limits in the majority of patients studied. For those with coronary artery disease the mean value was 65 (15) ms, and there was no relation to end diastolic pressure (correlation coefficient −0·04). In patients with mitral stenosis, the mean value was a little higher than normal (75 (20) ms), but this prolongation was not significant, and only one patient had a value above the 95% confidence limit of normal. In patients with aortic valve disease, the mean was 45 (20) ms, which again was not significantly different from normal. In patients with atrial fibrillation Q-MVC varied little from beat to beat when the RR interval was greater than 400 ms. For values lower than this, Q-MVC increased by 20–30 ms as the RR interval decreased to 300 ms.

Peak rate of rise of apexcardiogram—In patients with coronary artery disease, the Q to peak dA/dt interval had a mean value of 95 (25) ms. Nevertheless, the scatter was wide, and there was no significant correlation with end diastolic pressure, the value being 100 (25) ms in those in whom the end diastolic pressure was raised and 90 (20) in those in whom it was normal. When individual patients were considered, 15 out of 17 with normal end diastolic pressure had values within the normal range; this was the case in only 15 of those in whom end diastolic pressure was raised, the interval Q to peak dA/dt being abnormally prolonged in the remainder ($p<0.025$ with respect to patients with normal end diastolic pressure). Mean values of Q to peak dA/dt for patients with mitral and aortic valve disease were 90 (20) and 90 (15) ms, within the 95% confidence limits of normal. In patients with atrial fibrillation, the morphology of the first derivative of the apexcardiogram was sometimes abnormal, showing a bifid appearance, with the first peak preceding and the second following mitral valve closure. When the RR interval was very short the height of the first peak was regularly greater than that of the second. When a series of beats was studied over a range of RR intervals, it was apparent that the second peak seen after a short RR interval corresponded to the single one when the preceding interval was longer.

Isovolumic contraction time—This did not prove to be a discriminating measurement. For patients with coronary artery disease the mean value was 40 (20) ms, for those with mitral valve disease 40 (15) ms, and in the minority of those with aortic valve disease in whom aortic valve opening could be adequately displayed 40 (30) ms. None of these values was significantly different from normal. There was no significant relation with end diastolic pressure (correlation coefficient −0·1).

Relation between the timing of mitral closure and the peak rate of rise of the apexcardiogram—In patients with coronary artery disease and a normal left ventricular end diastolic pressure, there was a close correlation between the intervals Q-MVC and Q to peak dA/dt, given by the relation: Q to peak dA/dt=0·77(Q-MVC)+40 ms. The correlation coefficient was 0·76 and standard error of the estimate 9 ms (Fig. 3). The standard error of the slope was 0·17 and of the intercept 10 ms. Neither of these latter values was significantly different from those of the corresponding relation in normals. In patients in whom end diastolic pressure was raised, this relation was virtually lost, with values occurring earlier or later than normal. These deviations were most likely to occur when the interval Q to peak dA/dt was prolonged. In these patients, the overall correlation coefficient was 0·33. In patients with mitral stenosis, mitral valve closure was delayed with respect to peak dA/dt in four patients and was within the 95% confidence limits of normal for the remainder. By contrast, in aortic regurgitation, mitral closure was early in all but one case, occurring before the Q wave of the electrocardiogram in two (Fig. 4). In patients with atrial fibrillation, the relation between Q-MVC and Q to peak dA/dt could be studied over a wide range of RR intervals. In individual patients (Fig. 5) correlation coefficients ranged from 0·55 to 0·96 (median 0·79) for those in whom the mitral valve was normal and from 0·34 to 0·97 (median 0·87) in those with mitral stenosis. In 10 of the 14 patients in whom a significant correlation was present, the slope and intercept of the regression line were within the 95% confidence limits of normal. In the remainder, all of whom had mitral stenosis, the slope was significantly steeper, and the intercept lower than normal. In the absence of an "a" wave, the C point of the apexcardiogram was more clearly defined so that the interval Q-C could be measured. This was found to vary with Q-MVC, with correlation coefficients between 0·22 and 0·98 (median 0·87) in patients with mitral valve disease and 0·28 and 0·80 (median 0·57) in those without.

Discussion

Using simple non-invasive methods it is possible to study the relation between mechanical events at the onset of ventricular systole and mitral valve closure.

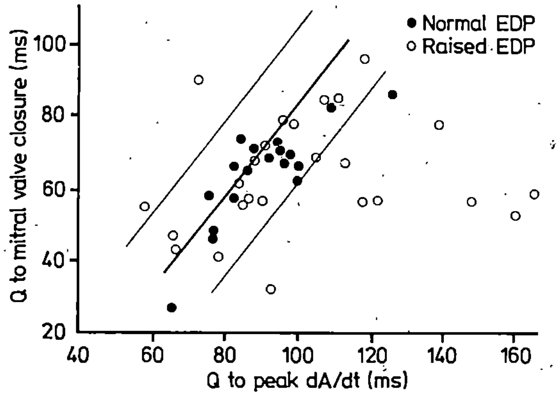

Fig. 3 *Relation between the intervals Q to mitral valve closure and Q to peak dA/dt for patients with coronary artery disease. The regression line and 95% confidence limits are derived from normal subjects. EDP, end diastolic pressure.*

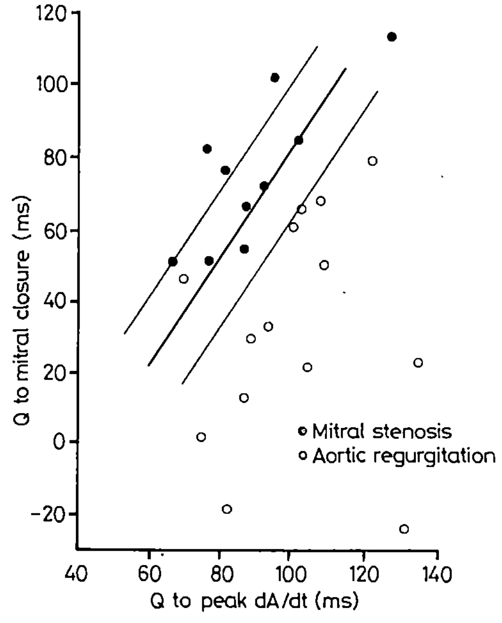

Fig. 4 *Relation between the intervals Q to mitral closure and Q to peak dA/dt for patients with mitral stenosis (●) and chronic aortic regurgitation or mixed aortic valve disease (○). Regression line and 95% confidence limits are derived from normal subjects.*

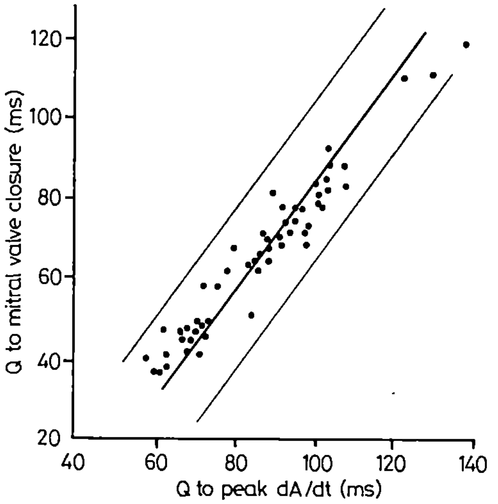

Fig. 5 *Beat to beat variation in the relation between the time intervals Q to mitral valve closure and Q to peak dA/dt in a single patient with atrial fibrillation and a normal mitral valve. The regression line and 95% confidence limits are derived from normal subjects.*

The timing of the upstroke of the apexcardiogram has been shown to be closely related to that of the intraventricular pressure pulse, subject to a delay of approximately 10 ms.[2 3] The onset of the apexcardiogram itself proved to be difficult to identify particularly when there was a significant "a" wave, but we found that the timing of the peak rate of rise of the apexcardiogram was a reproducible landmark. In the occasional patient, particularly in atrial fibrillation when the previous RR interval was short, there was more than one peak present. These ambiguities could, however, be clarified with reference to complexes preceded by a slightly longer RR interval. The timing of mitral valve closure was determined by M mode echocardiography. We found it essential to demonstrate clear cusp apposition, a pattern which M mode records directed from the cross sectional display showed to be obtainable from only a small region of the valve at the site of coaptation.

Previous observations have suggested that mitral valve closure is delayed when left atrial pressure is raised. This is the basis of prolongation of the interval from the Q wave of the electrocardiogram to the first heart sound reported many years ago in mitral stenosis.[4–6] Nevertheless, more recent studies,[6] particularly when simultaneous pressures and phonocardiograms are recorded, have shown this association to be weak and of little predictive value in individual patients. Our own results are in line with these more recent results, showing delay in mitral valve closure in only one of 10 patients with mitral stenosis. The interval from Q to mitral closure has also been measured by M mode echocardiography in patients in whom the mitral valve is normal,[7 8] incorporated into an index which also includes the period from aortic valve closure to maximum mitral valve opening (E point), and used to estimate left atrial pressure. Nevertheless, when we considered the interval from Q to mitral closure in isolation we found no correlation with left ventricular end diastolic pressure. The same applied for isovolumic contraction time whose variability in normal subjects was considerable, so that although our estimates agreed closely with those of Hirschfeld *et al*,[9] we found that no consistent alteration could be demonstrated in disease. Rather surprisingly, the interval from Q wave to peak rate of rise of the apexcardiogram did appear to have some sensitivity in detecting patients with a raised end diastolic pressure, being within normal limits in all but two cases in whom end diastolic pressure was normal but prolonged in 12 of 27 in whom end diastolic pressure was raised. This increase was associated with prolongation of the pre-ejection period and thus was more likely to have been due to the effects of inco-ordinate contraction[10] rather than any direct effect of left atrial pressure, stressing that systolic and diastolic left ventricular involvement frequently occur together in patients with coronary artery disease.

The apparent variability in the timing of mitral valve closure was considerably reduced when it was considered in relation to that of the peak rate of rise of the apexcardiogram. In common with Drui *et al*,[11] we found a significant correlation between the timing of these two events in normal subjects. An indistinguishable relation was present in patients with atrial fibrillation and a normal mitral valve and in patients with coronary artery disease in whom end diastolic pressure was normal. In rheumatic mitral stenosis, mitral valve closure was delayed with respect to the apexcardiogram in three out of 10 patients. When atrial fibrillation was present delayed mitral closure was more obvious when the preceding RR interval was long, leading to a significant increase in the slope of the relation between Q-MVC and Q to dA/dt. By contrast, mitral valve closure was early in the majority of patients with pure aortic regurgitation, or mixed aortic valve disease, measured with respect to the timing of the peak rate of rise of the apexcardiogram. Although premature mitral valve closure is well recognised as occurring in patients with aortic regurgitation, its appearance is usually held to be uncommon and when present to suggest that the lesion is acute in onset, severe, and requiring urgent operation.[12 13] Our results indicate that a lesser degree of prematurity in mitral valve closure is common in patients with chronic and well compensated disease. Its mechanism in these latter patients did not seem to be the same as that in acute regurgitation since in all but two cases mitral valve closure occurred after the Q wave of the electrocardiogram and in all but three after the onset of systolic contraction of the left ventricle. In chronic aortic regurgitation, therefore, the time relation between mitral closure and the onset of ventricular systole is altered, possibly as a result of the regurgitant jet from the aortic root. In patients with ischaemic heart disease and an increase in end diastolic pressure the normal close relation between mitral valve closure and peak dA/dt was lost owing to wide scatter rather than to any consistent alteration in timing.

These results have several consequences in interpreting early systolic events. Even in normal subjects there is considerable variability in the interval from the Q wave of the electrocardiogram to mitral valve closure. This appears to result directly from a corresponding variation in the onset of mechanical left ventricular systole as reflected in the upstroke of the apexcardiogram. The timing of peak dA/dt appears to be a useful landmark since its use allows that of mitral valve closure to be predicted within narrow limits. This relation persists in patients with atrial fibrillation in whom there is no mitral valve disease over a wide range of values, strongly suggesting that the timing of mitral valve closure depends on that of the onset of ventricular systole and not on left atrial contraction. The relation was also unaltered in patients with coronary artery disease, provided that end diastolic pressure was within normal limits, although mitral valve closure was frequently early with respect to the apexcardiogram when end diastolic pressure was raised. This occurred in spite of the interval from Q to mitral valve closure itself being within normal limits, indicating the increased sensitivity with which abnormalities could be detected if cusp motion is not considered in isolation but correlated with mechanical events. Although it might be predicted that an increase in left ventricular end diastolic and left atrial pressures might cause isovolumic contraction time to be shortened, by analogy with the clear cut effect of these abnormalities on isovolumic relaxation,[14] we found no evidence of this. The failure of the interval Q-MVC on its own to predict left ventricular end diastolic pressure suggests that the sensitivity of the more complex index must be due to changes in its other component, the time between A_2 and the E point of the mitral echogram. This latter interval includes isovolumic relaxation time, previously shown to be a sensitive index of end diastolic pressure in patients with coronary artery disease.[14] The relation with mitral valve closure may also be of value in interpreting the apexcardiogram. The interval from Q to peak dA/dt has been used to assess left ventricular systolic function since it has been found to correlate with the corresponding interval derived from the high fidelity pressure trace.[15-17] The morphology of the first derivative of the apexcardiogram may be atypical, however—showing two or more peaks of nearly equal height—making such measurements ambiguous. Our results suggest that this problem might be resolved by taking the peak following rather than preceding mitral valve closure. Finally, there has been much controversy in published reports on whether mitral valve closure[18] or the initial development of tension in ventricular myocardium[19] is responsible for the genesis of the first heart sound. This might be yet another field in which the close relation between early systolic events shown in the present study might be relevant, stressing the potential value of considering the interaction between valve motion and tension development rather than attempting to study each in isolation.

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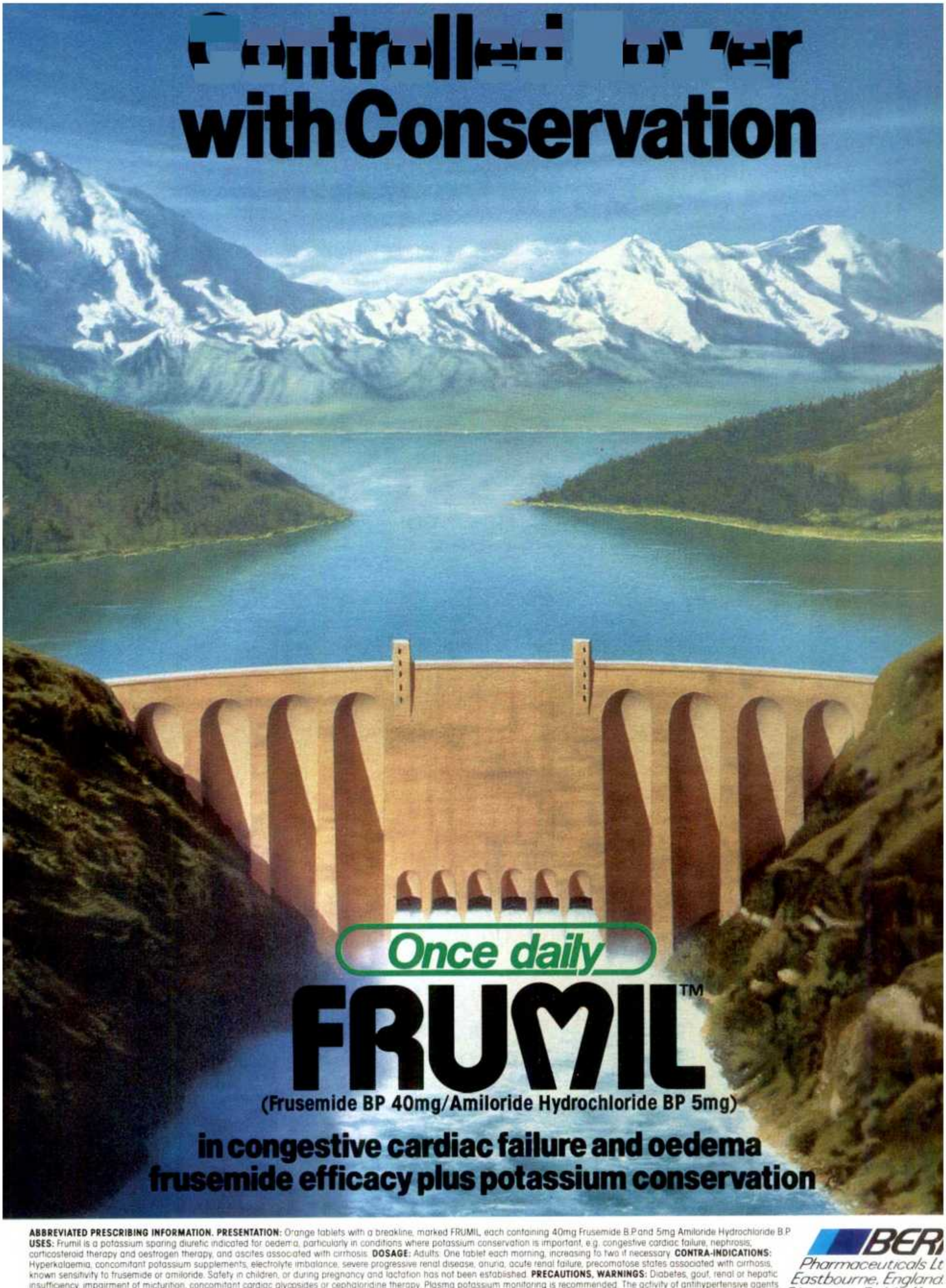
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Br Heart J 1985; 53: 443–50

Mustard's operation for patients with ventriculoarterial concordance
Report of two cases and a cautionary tale

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SUMMARY Three patients with ventriculoarterial concordance and an abnormal atrioventricular connexion were investigated. One patient had total anomalous pulmonary venous connexion to a left vertical vein. In 1972 this was repaired and a ventricular septal defect was closed, but the presence of atrioventricular discordance was missed and the patient died. In the other two patients, Mustard's operation resulted in survival. One patient had situs solitus and atrioventricular discordance with an associated ventricular septal defect, which was closed. The other had left isomerism (quasi solitus) with an ambiguous atrioventricular connexion (quasi discordant). A previously noted ventricular septal defect had spontaneously closed.

Intra-atrial baffle procedures (venous switches) such as Mustard or Senning operations are normally used to compensate congenitally determined single switches in the circulation. By far the commonest of these is complete transposition, in which the patient has a single switch (ventriculoarterial discordance with atrioventricular concordance). A much rarer indication for venous switching occurs when the single switch is at atrioventricular level and there is no switch at ventriculoarterial level—that is, there is ventriculoarterial concordance. In fact, only eight such operations have been hitherto described.[1-6] The purpose of this report is to document two further examples and to illustrate the danger of an incorrect preoperative diagnosis in a third.

Patients and methods

CASE 1

A 3½ year old girl was referred from Germany with a diagnosis of total anomalous pulmonary venous connexion. The angiocardiograms on which this diagnosis was based were not of high quality, but on reviewing them it was clear that there was situs solitus with atrioventricular discordance and ventriculoarterial concordance, a ventricular septal defect, and total anomalous pulmonary venous connexion to a left vertical vein. The ventricles were normally related for atrioventricular discordance, but the great arteries were side by side with the aorta to the right.

On physical examination, she had moderate cyanosis and finger clubbing. There was clinical hypertrophy of both ventricles and a systolic thrill at the lower left sternal border. On auscultation, the first heart sound was normal, the second heart sound was split, and there was a pansystolic murmur at the lower left sternal border. There was no diastolic murmur and no sign of heart failure. Her chest *x* ray film showed a large heart with increased pulmonary vascular markings and a wide mediastinum, and her electrocardiogram showed sinus rhythm and right atrial hypertrophy with a PR interval of 0·16 s, a QRS interval of 0·10 s, and a somewhat atypical right bundle branch block pattern.

Diagnosis

She underwent repeat cardiac catheterisation in June 1972. The vertical common pulmonary vein was entered and contained blood with an oxygen saturation of 92%. There was a 10 mm Hg mean pressure gradient between the vertical vein and the superior vena cava. Both ventricular systolic pressures were equal at 90 mm Hg and the pulmonary artery pressure was 75/40 mm Hg. The pulmonary and systemic artery oxygen saturations were equal (80%). Repeat cineangiograms were performed with injection into

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the common pulmonary vein, pulmonary trunk, and left sided ventricle, but a fault in processing destroyed the frontal plane film. She was therefore referred for surgery with a diagnosis of situs solitus with normal cardiac connexions, total anomalous pulmonary venous connexion to a vertical vein, and a ventricular septal defect.

Operation

At operation a ventricular septal defect 2 cm in diameter was closed through the right atrioventricular valve. An anastomosis was constructed between the pulmonary venous confluence and the left atrium, and a patent foramen ovale was closed. The common pulmonary vein was ligated. She could not be weaned from cardiopulmonary bypass despite an attempt to reopen the ventricular septal defect, and she died on the operating table.

Necropsy findings

At necropsy, the reason for the operative death became clear. The bronchi and atria were in situs solitus. Pulmonary venous return had been successfully directed to the left atrium and a patent foramen ovale closed, but these two procedures had been disastrous in the presence of atrioventricular discordance with ventriculoarterial concordance. The right sided mitral valve had two sets of papillary muscles and no insertion into the septum.

There was a large perimembranous ventricular septal defect excavating both inlet and outlet septa, such that posteriorly it was roofed by the two atrioventricular valves in continuity, and anteriorly it was roofed by the outlet septum. Into the underside of this was inserted the anteroseptal commissure of the tricuspid valve (the remainder of which was normal). There was mild malalignment of the trabecular and outlet septa such that the aortic valve overrode the septum slightly, originating 85% above the left ventricle.

There was a bilateral infundibulum, with 7 mm of muscle separating the mitral and aortic valves and 5 mm of muscle separating the tricuspid and pulmonary valves. The great arteries lay side by side with the aorta to the right—that is, with a slight clockwise spiral as they ascended. The right ventricle was a little small, being only two thirds the length of the left ventricle, and lay to its left, the septal orientation being as is usually found in congenitally corrected transposition. The coronary artery pattern was inverted.

CASE 2

A 4 month old baby boy, weighing 5·2 kg, was admitted to our unit in congestive heart failure. Poor feeding and moderate cyanosis at rest had been noted since birth. On examination the child was dyspnoeic and severely cyanosed on crying. His pulse rate was 145 beats/minute and his blood pressure 100/60 mm Hg. On auscultation no cardiac murmurs were detected. His chest was clear. There was no hepatomegaly, and all peripheral pulses were palpable. Laboratory investigations showed a haemoglobin concentration of 17·7 g/dl and a packed cell volume of 51%. His chest radiography showed pulmonary plethora with mild cardiomegaly, and his electrocardiogram recorded sinus rhythm, right axis deviation, and a deep Q wave in leads II, III, aVF and V4R. There was a dominant R wave in V4R with an upright T wave.

Diagnosis

Cardiac catheterisation and angiocardiography showed situs solitus, atrioventricular discordance, ventriculoarterial concordance, ventricular septal defect, and patent foramen ovale. The great arteries were normally related, spiralling clockwise as they ascended. There was a very short muscular subaortic infundibulum and a longer subpulmonary infundibulum. The intracardiac pressures were: mean right atrium 3 mm Hg, mean left atrium 14 mm Hg, right ventricle 70/0 mm Hg, left ventricle 70/0 mm Hg, pulmonary artery 70/30 (mean 42) mm Hg, and systemic artery 70/50 (mean 60) mm Hg. The aortic oxygen saturation was 54% and improved to 66% after balloon septostomy. The pulmonary artery oxygen saturation before septostomy was 92%. In view of the severe degree of arterial desaturation and failure to thrive, it was decided to proceed to surgical correction.

Operation

After the pericardium had been opened the anatomy of the heart was assessed. The heart was enlarged. The pulmonary artery was anterior and to the left of the aorta, which was posterior and to the right. Both venae cavae were normally connected with the right atrium, which was on the right. The right atrium was connected to the morphologically left ventricle. The pulmonary veins emptied into the left atrium, which drained to the somewhat superior and leftward morphologically right ventricle. There was only one large coronary artery arising from the aorta anteriorly, giving off the left and the right coronary arteries which were distributed on the anterior aspect of the heart. After cannulation of the aorta and both venae cavae, cardiopulmonary bypass was established. The patient was cooled to 20°C nasopharyngeal temperature, the aorta was cross clamped, and cardioplegic solution was infused. The right atrium was opened and it was possible to confirm the angiographic diagnosis. The ventricular septal defect was located in the inlet septum and was closed through a short right ven-

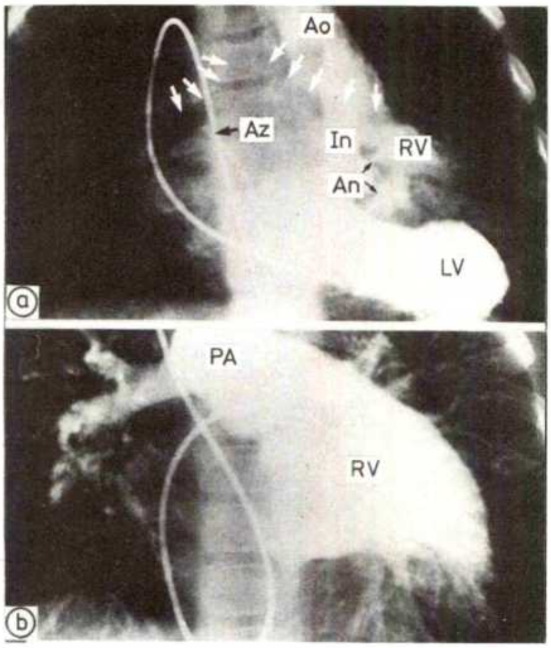

Fig. 1 *Case 3: left ventricular angiocardiograms (frontal plane). (a) Shows the catheter passing round an azygos continuation (Az) into the right sided atrium and thence to the left ventricle (LV), from which the aorta (Ao) opacifies via a subaortic infundibulum (In). An aneurysm (An) of the membranous septum is seen, through which two tiny ventricular septal defects (small black arrows) opacify the right ventricle. Note the two long morphologically left bronchi (white arrows). (b) Shows the catheter, having crossed a patent foramen ovale, entering the right ventricle (RV), from which the pulmonary trunk (PA) opacifies.*

triculotomy using a Dacron patch. Anteriorly the stitches were inserted on the morphological right side of the ventricular septum, according to the technique previously described to reduce the risk of injuring the His bundle.[7] Mustard's operation was then performed using a pericardial patch. The new pulmonary venous atrium was enlarged with a woven Dacron patch. When perfusion was terminated the patient was in sinus rhythm. Postoperative systolic pressures were: aorta 100 mm Hg and pulmonary artery 30 mm Hg. The postoperative course was uneventful, and the patient was discharged two weeks later in an excellent condition.

Follow up

After almost six years the patient was still asymptomatic and in sinus rhythm. Recatheterisation in January 1984 showed normal intracardiac pressures with no residual shunts and no evidence of caval pathway obstruction. A cross sectional echocardiogram showed typical atrioventricular discordance, with reversed offsetting of the atrioventricular valves. Precordial short axis views showed the typical "circle and sausage" appearance of normally related great arteries, the aorta being the circle and the right ventricular outflow tract and pulmonary trunk being the sausage.

CASE 3

A male child had had cyanosis and dyspnoea since the age of 2 weeks. Cyanosis and clubbing increased progressively, while exercise tolerance gradually decreased. At the age of 12 years he was investigated abroad. The diagnosis of transposition of the great arteries with a small ventricular septal defect and interruption of the inferior vena cava with right azygos continuation was made. Pressures at the time of cardiac catheterisation were equal in the two atria (mean 7 mm Hg). The pressure in the subpulmonary ventricle was 24/0–5 mm Hg and in the pulmonary artery 22/7 mm Hg. The systolic pressure in the subaortic ventricle and aorta was 110 mm Hg. The pulmonary artery oxygen saturation was 86%, whereas that in the frontal artery was 72%.

The patient was lost to follow up. At 16 years of age he was referred to us for further evaluation and treatment. On examination, he was physically underdeveloped, with severe cyanosis and clubbing and was dyspnoeic at rest. His blood pressure was 120/60 mm Hg. There was an ejection systolic murmur at the left sternal border and a split second heart sound. His chest was clear on auscultation. His liver was enlarged to 4 cm below the costal margin. The spleen was not palpable. All peripheral pulses were palpable and equal. Laboratory investigations showed a haemoglobin concentration of 22·8 g/dl and packed cell volume of 72%. Coagulation tests and serum electrolyte and blood urea concentrations were all within normal limits. His chest radiograph showed mild cardiomegaly with a cardiothoracic ratio of 0·54 and increased pulmonary vascular markings. His electrocardiogram recorded a superior P wave axis with right axis deviation and right bundle branch block.

Diagnosis

A review of the angiocardiograms (Fig. 1) established a diagnosis of left atrial isomerism (quasi solitus), ambiguous (quasi discordant) atrioventricular connexion, ventriculoarterial concordance, left hand pattern of ventricular morphology, small ventricular septal defect in the aneurysm of the ventricular septum, aberrant right subclavian artery, atrial septal defect at the fossa ovalis, and interruption of the inferior vena cava with azygos continuation to the right superior vena cava. The pulmonary valve lay anterior to the right of the aorta, and the great arteries spiralled counterclockwise as they ascended.

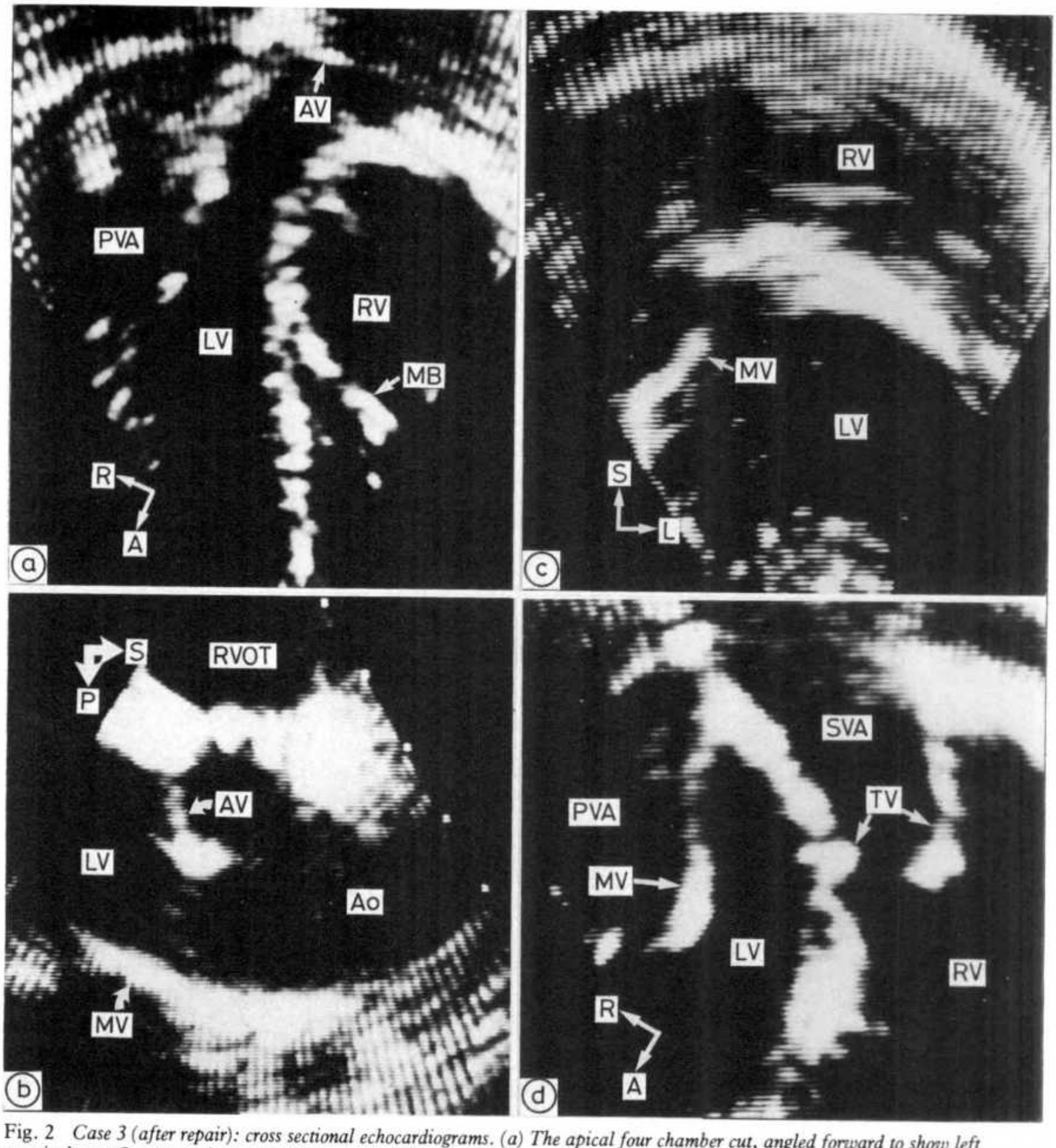

Fig. 2 *Case 3 (after repair): cross sectional echocardiograms. (a) The apical four chamber cut, angled forward to show left ventricular outflow tract, shows the right ventricle (RV) identified as such by the moderator band (MB). The pulmonary venous atrium (PVA) is now connected to the left ventricle (LV), which has a normal outflow tract roofed by the aortic valve (AV). (b) The parasternal long axis cut looks remarkably normal. Note the mitral valve (MV) and right ventricular outflow tract (RVOT). Other abbreviations as above. (c) The subcostal paracoronal cut shows the right ventricle (RV) above the left ventricle (LV). The mitral valve (MV) separates the LV from what used to be the right sided morphologically left atrium. (d) The apical four chamber cut shows pronounced reversed offsetting of the mitral (MV) and tricuspid (TV) valves. Other abbreviations as above. A, anterior; L, left; R, right; S superior.*

Operation

At operation a midline sternotomy was performed and the pericardium resected for a patch. The outside anatomy of the heart was as expected from angiocardiography. Both atria were of left morphology. The heart was moderately enlarged. The pulmonary artery

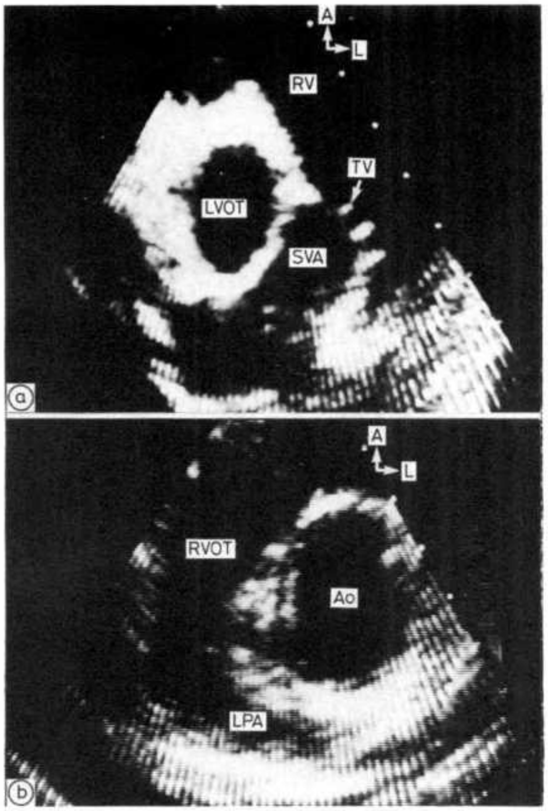

Fig. 3 *Case 3: cross sectional echocardiograms in the parasternal short axis cuts showing (a) the systemic venous atrium (SVA), formerly the left sided left atrium, draining via the tricuspid valve (TV) to the right ventricle (RV), which winds around the left ventricular outflow tract (LVOT); and (b) at a slightly higher level, the right ventricular outflow tract (RVOT) leading out to the pulmonary trunk and left pulmonary artery (LPA), which partly encircle the aorta (Ao). Note that these short axis views are orientated more or less as the mirror image of normal, indicating counterclockwise spiralling great arteries. A, anterior; L, left.*

ascended to the right of the aorta, having arisen from the left sided morphologically right ventricle. The aorta was posterior and to the left, arising from the inferior and right sided morphologically left ventricle. The superior vena cava and hepatic veins entered the right sided morphologically left atrium, which was connected to the morphologically left ventricle, while the left sided morphologically left atrium received the pulmonary veins and emptied into the morphologically right ventricle.

In view of the rather small volume of the right sided left atrium, it was decided to perform the Mustard rather than the currently favoured Senning operation. After cannulation of the aorta, superior vena cava, and common hepatic vein, cardiopulmonary bypass was started and the patient cooled to 20°C nasopharyngeal temperature. The aorta was cross clamped and cardioplegia solution was infused to the root of the aorta. The right sided atrium was opened and the anatomy visualised. The right sided atrium opened into the morphological left ventricle through a valve which had all the characteristics of a mitral valve. The remnant of the atrial septum was resected and then the left atrioventricular valve visualised. It was a tricuspid valve. A ventricular septal defect was not found after careful inspection of the ventricular septum. It was therefore assumed that it had closed in the four years between cardiac catheterisation and operation. Mustard's operation with the modifications as usually practised in our unit[8] was then performed. When completed, the cross clamp was removed, air evacuated from the heart, the patient rewarmed, and perfusion discontinued. At the end of the operation, the patient was in sinus rhythm with the following pressures: right ventricular systolic 40 mm Hg, pulmonary artery systolic 35 mm Hg, left ventricular systolic 80 mm Hg, aortic systolic 80 mm Hg, superior vena caval mean 12 mm Hg, and pulmonary venous atrial mean 10 mm Hg.

His postoperative progress was entirely uneventful and he was discharged two weeks postoperatively to return home. Before discharge, a cross sectional echocardiogram showed typical features of ventricular inversion, except that there was ventriculoarterial concordance. Parasternal short axis cuts appeared as a mirror image of the normal appearance, because of the counterclockwise spiralling of the great arteries (Figs. 2 and 3).

Discussion

These patients illustrate clearly the two ways in which the pulmonary and systemic circulations can be switched at atrioventricular level. The first two patients had atrioventricular discordance in that the right atrium was connected to the left ventricle and the left atrium to the right ventricle. The third, who had two atria, both of which were morphologically left, can only be described as having an ambiguous atrioventricular connexion. In planning surgical repair, however, it was helpful to note that the pulmonary veins drained to the left sided atrium and the systemic veins to the right sided atrium and to treat the patient as if he had situs solitus with atrioventricular discordance. Strictly speaking, therefore, the segmental anatomy would be described as left isomerism (quasi solitus) with an ambiguous atrioventricular connexion (quasi discordant) and ventriculoarterial concordance.[9]

Both conditions described here are extremely rare, Table *Details of patients in the present study and in previous reports with ventriculoarterial concordance and atrioventricular discordance or quasi concordance*

Case No	*Reports*	*Age*	*Apex*	*Situs*	*AV connexion*	*Great arteries*	
						Spiral	*Ao–PA*
1	Lev,[23] van Praagh[24]	4 wk	L	Solitus	Discordant	Clockwise	R
2	Lev,[23]	12 yr	L	Solitus	Discordant	Parallel	AR
3	van Praagh[25]	4 mnth	L	Solitus	Discordant	Clockwise	PR
4	Espino-Vela[13]	19 yr	L	Inversus	Discordant	Clockwise	PR
5	Clarkson[1]	2 yr	R	Inversus	Discordant	Clockwise	PL
6	Anderson[26]	3 mnth	R	Inversus	Discordant	?Parallel	AL
7	Squarcia[27]	1 yr	R	Inversus	Discordant	Clockwise	PR
8	Quero-Jimènez[28]	7 mnth	L	Solitus	Discordant	Clockwise	PR
9	Quero-Jimènez[28]	5 mnth	L	Solitus	Discordant	Clockwise	PR
10	Fox[2]	?	R	Inversus	Discordant	?	?
11	Fox[2]	?	L	Solitus	Discordant	?	?
12	Zakheim[29]	4 wk	L	Solitus	Discordant	Parallel	AR
13	Hazan[3]	9 yr	R	Quasi inversus	Quasi discordant	Clockwise	PL
14	Attie[20]	?	L	Solitus	Discordant	?Counterclockwise	PL
15	Attie[20]	?	L	Solitus	Discordant	?Counterclockwise	PL
16	Attie[20]	?	L	Solitus	Discordant	?Clockwise	PR
17	Attie[18]	4 mnth	L	Solitus	Discordant	Clockwise	PR
18	Leijala[6]	4 mnth	R	Inversus†	Discordant†	Clockwise	PR
19	Calabrò[10]	2 mnth	R	Solitus	Discordant	Clockwise	PR
20	Ostermeyer[4]	10 yr	R	Solitus‡	Discordant‡	?	PL
21	Ostermeyer[4]	10 mnth	L	Solitus	Discordant	Clockwise	PR
22	Snider[5]	3 wk	L	Solitus	Discordant	Clockwise	PR
23	Present report	3½ yr	L	Solitus	Discordant	Clockwise	R
24	Present report	4 mnth	L	Solitus	Discordant	Clockwise	PR
25	Present report	16 yr	L	Quasi solitus	Quasi discordant	Counterclockwise	PL

AL, anterior and leftward; AR, anterior and rightward; ASD; atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; Acc, accessory; CAVO, common atrioventricular orifice; Coarc, coarctation of the aorta; Cont, continuation; IVC, inferior vena cava; L, left; LAVV, left atrioventricular valve; LJAA, left juxtaposition of the atrial appendage; MS, mitral stenosis; MV, mitral valve; PA, pulmonary artery; PAPVC, partial anomalous pulmonary venous drainage; PDA, persistent ductus arteriosus; PL, posterior and leftward; PR, posterior and rightward; PS, pulmonary stenosis; R, right; RA, right atrium; RAA, right aortic arch; RJAA, right juxtaposition of the atrial appendage; RV, right ventricle; SAS, subaortic stenosis; TAHVC, total anomalous hepatic venous connexion; TAPVC, total anomalous pulmonary venous drainage; TV, tricuspid valve; VSD, ventricular septal defect.

*Architectural pattern.

†Possibly quasi inversus and quasi discordant.

‡Possibly quasi solitus and quasi discordant.

there being only 22 reports so far published in the English language (Table). Since both are associated with a single switch in the circulation both may be confused clinically with complete transposition of the great arteries. The irony of our first case is that because total anomalous pulmonary venous return resulted in equalisation of the systemic and pulmonary arterial oxygen saturations, and angiocardiography was suboptimal, neither complete transposition nor isolated atrioventricular discordance[10] was suspected preoperatively. Careful evaluation of the angiocardiograms with particular attention to the ventricular morphology should have established the correct diagnosis. Though cross sectional echocardiography was undertaken only postoperatively and only in two patients, the features were sufficiently striking to suggest that the diagnosis could have been reached before cardiac catheterisation, as reported by Snider and colleagues.[5]

The Table lists those patients in English language reports with a similar sequential chamber organisation. Three cases previously designated as having "isolated ventricular inversion"[11] or "ventricular inversion without transposition[12 13] have not been included since they definitely or almost certainly had an absent atrioventricular connexion.

The first step in the diagnosis of atrioventricular discordance is to establish atrial situs.[14] This is not as easy as it seems. In Clarkson's case there was situs solitus of the abdominal viscera and situs inversus of the atria and bronchi.[1] In our third case, the bronchial pattern[15 16] and atrial appendage morphology as seen at operation indicated left atrial isomerism. This leads us to suspect that the case of Hazan and colleagues[3] had left isomerism rather than situs inversus. There was an azygos continuation of the inferior vena cava on the left, a common atrium, and a complete atrioventricular septal defect, all commonly associated with left isomerism.[9] In the lateral angiocardiogram, both pulmonary arteries looped posterior to the trachea, a pattern described by Soto and colleagues as characteristic of left isomerism.[17] Similar, but not so clear cut, considerations apply to the heart described by Leijala and colleagues[6] and the first case of Ostermeyer and colleagues.[4]

Thus some diversity exists at the atrioventricular junction in these patients, with even a crisscross relation having been recorded.[18] There is even more

*Ventricular morphology**	*Mitral-aortic continuity*	*Associated defects*	*Treatment*	*Result*
L	No	Coarc, VSD, PDA	Medical	Died
L	?	VSD, PS	Modified baffles	Died
L	Yes	VSDs	PA banding	Died
R	?	TAPVC (RA), ASD, VSD, PS, MS	L Blalock shunt	Died
R	Yes	ASD	Mustard operation	Alive
R	No	VSD	Medical	Died
R	?	VSD	?	?
L	Yes	VSD, PDA, hypoplastic TV, supravalvar ring	Blalock-Hanlon shunt, PA banding	Died
L	Yes	VSD, RJAA, hypoplastic RV	Medical	Died
R	?	VSD	Mustard, VSD closed	Alive
L	?	VSD, PAPVC	Mustard, VSD closed	Died
L	No	RAA, acc MV tissue, SAS, VSD, PDA	PDA ligation, atrial septostomy	Died
R	Yes	Common atrium, CAVO	Mustard operation	Alive
L	?	?	?	?
L	?	?	?	?
L	?	?	?	?
L	?	Crisscross, LJAA, VSD, RV hypoplasia	Medical	Died
R	?	Hemiazygos cont on left, TAHVC (RA)	Mustard operation	Alive
L	Yes	Straddling TV, SAS, VSD, Coarc, PDA	Medical	Died
L	Yes	AVSD, partitioned orifices, PAPVC, TAHVC (right sided atrium)	Mustard, LAVV repair	Alive
L	Yes	VSD	Mustard, VSD closed	Alive
L	Yes	VSD	Senning operation	Alive
L	No	VSD, TAPVC	Repair of TAPVC	Died
L	No	VSD, PFO	Mustard, VSD closed	Alive
L	Yes	Aneurysm, membranous septum, interrupted IVC, azygos cont, right aberrant, right subclavian artery	Mustard operation	Alive

diversity at the ventriculoarterial junction, despite the fact that all have ventriculoarterial concordance. Firstly, there is the question of mitral-aortic continuity or discontinuity. This seems of relatively small importance, particularly in the light of the wide range of normality which exists in normal hearts.[19] Of considerably more importance, particularly to the echocardiographer, is the relation of the great arteries. If the aorta is posterior and the great arteries spiral clockwise, then the parasternal short axis cut or scan will show the "sausage", corresponding to the right ventricular outflow tract and pulmonary trunk, in its normal position to the left of the "circle", the aorta. On the other hand, if (as in Fig. 3) they spiral counterclockwise the picture obtained will be the mirror image of this. Therefore it is vital to ensure that left-right orientation is correct when the echocardiogram is recorded.

As the Table shows, whether or not there is situs solitus or inversus the great arteries almost always in fact spiral clockwise. In fact, our third case is the first reported in which the arteries definitely spiralled counterclockwise, though this was probably the arrangement in two cases described by Attie and colleagues.[20] Given that clockwise spiralling of the great arteries is the norm, whatever the atrial situs, the frailty of qualifying such terms as ventricular or atrial inversion or non-inversion, ventricular discordance, or atrioventricular discordance with the adjective "isolated"[1 10 21] becomes immediately obvious. After all, what should be regarded as the normal relation of the great arteries in, for example, situs solitus with atrioventricular discordance and a left hand pattern of ventricular architecture? Is it determined by the atrial situs or the ventricular architecture? If the atrial situs is the determinant, then isolated ventricular inversion implies clockwise spiralling, whereas if ventricular architecture is the determinant, isolated ventricular inversion implies parallel or counterclockwise great arteries. The concept of chirality was emphasised by van Praagh *et al* with relation to atrial and ventricular architecture, when they pointed out, for example, that a normal right ventricle (in a D-loop) cannot be superimposed on an inverted right ventricle (in an L-loop), since one is a stereoisomer of the other.[22] Precisely the same argument applies to spiralling great arteries. Clockwise spiralling great arteries cannot be superimposed on counterclockwise ones. It is therefore difficult to believe that two hearts, both with situs solitus and atrioventricular discordance with a left hand pattern of ventricular architecture, are the result of the same disturbance of morphogenesis if in one heart the great arteries spiral clockwise and in the other counterclockwise. Though physiologically these hearts are identical, anatomically they are quite distinct.

Nevertheless, as far as surgical management of these conditions is concerned, spiralling of the great arteries is unimportant compared with correcting for the atrioventricular discordance or quasi discordance.

Even if the fact that single unsuccessful surgical case reports are rarely published is borne in mind, it is impressive that all patients save one who are reported to have an interatrial baffle procedure survived. Such a form of repair has the particular advantage that the morphological left ventricle remains supporting the systemic circulation.

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Normal intracardiac and great artery blood velocity measurements by pulsed Doppler echocardiography

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SUMMARY One hundred and 10 normal subjects were studied by pulsed Doppler velocimetry to determine the range of values of blood velocity across the cardiac valves and in the great vessels. Modal peak velocities of 1·55 m/s occurred in the left heart, but right heart peak velocities were lower. In most sites a statistically significant inverse relation between peak velocities and age or body surface area was found. Time to peak velcocity in the pulmonary artery and ascending aorta increased significantly with age and was shorter in the aorta than in the pulmonary artery. These data were developed to serve as standards for the assessment of values recorded in patients with congenital and acquired cardiac disease.

The Doppler shift of ultrasound can be used to determine blood velocity at a number of cardiac and vascular sites, and these data in turn may be used to calculate blood flows and pressure differences.[1–3] Several small series of patients with normal values have been reported. Hatle and Angelsen reported the results in 30 children and 40 adults, but no methodology was detailed.[4] Grenadier and colleagues reported values for a small group of children, but no effort was made to correct velocities for the elevational plane angle, and aortic velocities were not measured with currently available transducers which can record velocities parallel with blood flow in the ascending aorta.[5] Several other reports mention normal velocities or time to peak velocity at isolated sites.[6–8]

The purpose of this study was to determine the modal peak blood velocity and time to peak velocity for a normal population at several clinically important sites. A feature of this study is that all measurements were obtained after careful alignment of the ultrasound beam with flow in three planes.

Patients and methods

One hundred and 10 normal volunteers with no evidence of cardiac disease or other known chronic illness were studied. None had been referred for cardiac evaluation. Informed consent was obtained from each subject or from the parents of the younger children. All were studied at rest and without sedation by one of two examiners (NW or SJG). The ages of the subjects ranged from 14 days to 35 years (mean 11·6 years).

Each examination was performed with an instrument which combined range gated pulsed Doppler velocimetry and cross sectional imaging echocardiography (Honeywell Ultra Imager). Velocities were obtained by aligning the Doppler cursor with the expected direction of flow in the two visualised planes and then searching in these two planes for the signal with the highest velocity and least spectral dispersion. The transducer was then angled in the third, or elevational, plane to achieve the highest velocity with the least spectral dispersion.

The velocity thus obtained was considered to be the maximal velocity. This was measured from baseline (zero) velocity to the peak of the modal velocity, identified as the darkest point at the peak of the curve (Fig. 1a). This point was chosen in preference to the absolute maximum velocity seen at the peak for reasons which will be discussed. The mean of four or five complexes was recorded. Time to peak velocity was measured from the departure of the velocity curve from the baseline to the modal peak velocity. Modal peak velocity and time to peak velocity were recorded in the superior vena cava, the ascending aorta and descending aorta (from the suprasternal notch), the abdominal aorta (from the subxiphoid region), the inlet of the tricuspid and mitral valve (from the apical four chamber plane), and the main pulmonary artery

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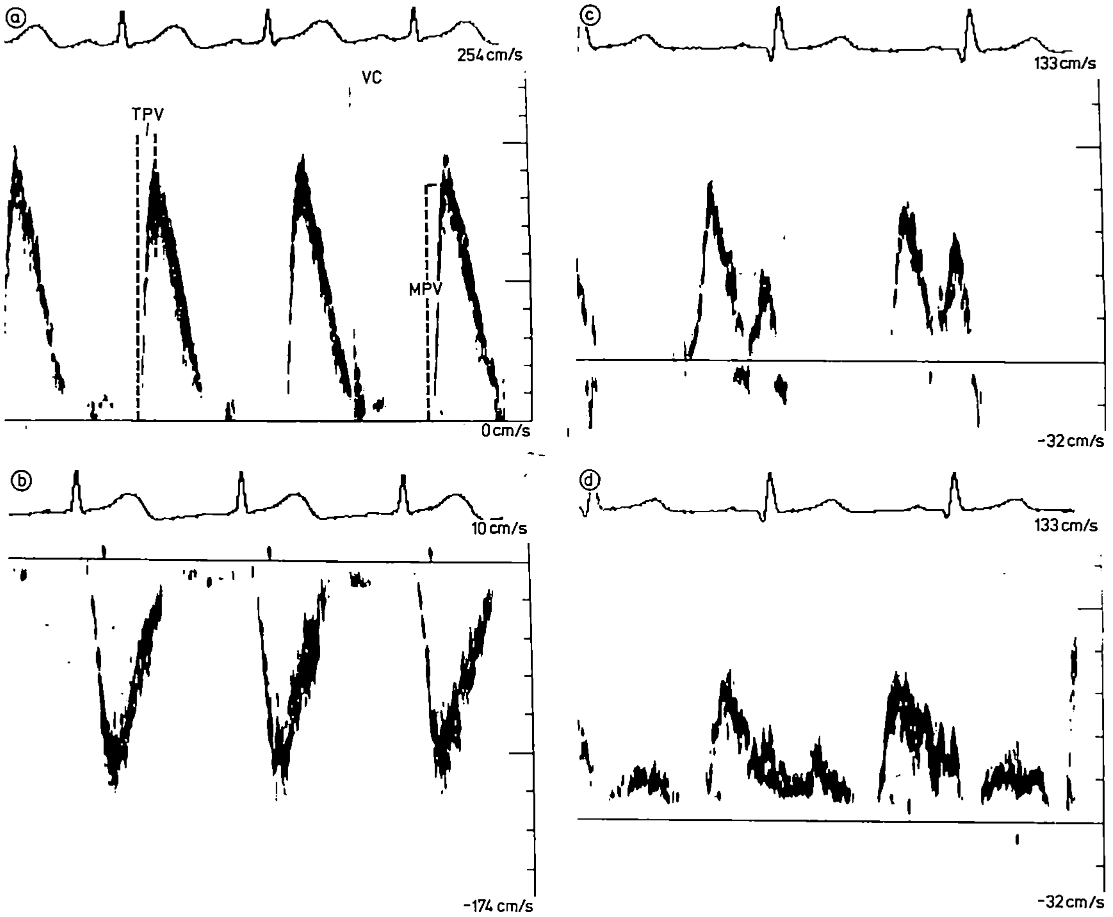

Fig. 1 *Pulsed Doppler echocardiograms showing a normal waveform (a) in the ascending aorta (viewed from the suprasternal notch), (b) in the pulmonary artery (parasternal short axis view); (c) across the mitral valve (apical four chamber view); and (d) across the tricuspid valve (apical four chamber view). (a) The Doppler frequency shift is converted to a velocity measurement in cm/s (vertical axis). A systolic waveform directed towards the transducer (positive wave) is present. The ascending limb of the wave is a discrete line indicating that at any given point all blood cells within the sample volume are travelling in the same direction at similar speed. At peak velocity there is some broadening of the line indicating blood cells travelling in differing directions and velocities. This feature is also apparent during the deceleration phase of the curve. The modal peak velocity (MPV) is the velocity that occurs most frequently and is identified as the darkest point on the peak of the curve. Time to peak velocity (TPV) is measured from the onset of the upstroke of the curve to the MPV as shown. VC, valve click. (b) A negatively directed systolic wave with characteristics similar to those in the aorta is present. (c) Two positively directed waves are present in diastole; the first and highest peak (from which modal peak velocity is measured) corresponds to the period of maximum mitral flow and the second coincides with the flow associated with atrial contraction. (d) The general configuration of the waveform is similar to that across the mitral valve but modal peak velocity is lower.*

immediately distal to the pulmonary valve (from the parasternal short axis view). Time to peak velocity and modal peak velocity were measured from the monitor at a sweep speed of 100 mm/s with electronic calipers. Subjects were not restudied by the other operator nor were measurements repeated at different times of the same day or on different days.

Although it was possible to record velocities from all other areas at an intercept angle of ≤20° in the two visualised planes, the abdominal aorta was always interrogated at an intercept angle of >20°. Therefore at this site velocities were corrected according to the

Table 1 *Modal peak velocity and time to peak velocity in the heart and great vessels in 110 subjects*

Site	*Range*	*Mean*	*Median*	*1 SD*
Modal peak velocity (cm/s)				
Superior vena cava	28–80	51	51	13
Tricuspid valve	33–81	53	51	12
Pulmonary artery	52–131	81	82	17
Mitral valve	44–128	77	78	16
Ascending aorta	76–155	104	103	19
Descending aorta	70–160	101	99	17
Abdominal aorta	55–222	113	107	30
Time to peak velocity (ms)				
Pulmonary artery	60–180	121	120	27
Ascending aorta	50–150	92	90	23
Descending aorta	50–190	107	110	28

formula: true velocity = recorded velocity/cosine theta, where theta is the angle at which the ultrasound beam intercepts the axis of blood flow.

STATISTICAL ANALYSIS

For each variable means and standard deviations were calculated. Scatter diagrams for all peak velocities and time to peak aortic and pulmonary velocities against age and body surface area were plotted and correlation coefficients and standard errors of the estimate determined assuming a linear relation. To facilitate statistical analysis for those subjects in whom complete data were not obtained the respective mean value of the peak velocity calculated from the remaining population for that variable was used. This method was not, however, used to complete data for the abdominal aorta because of the relatively large number of substitutions that would have been necessary. Altogether only 10 mean values were inserted accounting for <1% of the total data.

Results

The examination was generally completed without difficulty except for the recording of velocities from the abdominal aorta. It was possible to record velocities from this site in only 89 out of 110 subjects, and the angle in the visualised planes was often as large as 45° and at times even greater. Velocity recording also failed for the pulmonary artery in two subjects, for the ascending aorta in three, and for the descending aorta in five. Figure 1 shows examples of typical normal waveforms.

A normal distribution of modal peak velocity and time to peak velocity was observed at all sites. Table 1 shows the range of velocity at each site and the time to peak velocity (acceleration time) in the ascending aorta, the descending aorta, and the pulmonary artery. Figures 2–5 and Table 2 show the correlation

Table 2 *Correlation of modal peak velocities and time to peak velocity with body surface area and age*

Site	*Body surface area*			*Age*		
	r	*SEE*	*p value*	*r*	*SEE*	*p value*
Superior vena cava	−0·53	10·8	<0·001	−0·48	11·1	<0·001
Tricuspid valve	−0·22	12·2	<0·05	−0·25	12·1	<0·01
Pulmonary artery	−0·21	16·8	<0·05	−0·31	16·4	<0·01
Mitral valve	−0·27	15·3	<0·01	−0·39	14·7	<0·001
Ascending aorta	0·04	18·6	NS	−0·06	18·6	NS
Descending aorta	−0·07	16·9	NS	−0·04	16·9	NS
Time to peak velocity:						
Pulmonary artery	0·6	21·6	<0·001	0·61	21·4	<0·001
Ascending aorta	0·62	17·7	<0·001	0·53	19·2	<0·001
Descending aorta	0·57	23·3	<0·001	0·55	23·8	<0·001

SEE, standard error of estimate.

Table 3 *Correlation of modal peak velocity and time to peak velocity at different sites*

Site	*Modal peak velocity*						*Time to peak velocity*	
	SVC	*TV*	*PV*	*MV*	*Ascending aorta*	*Descending aorta*	*PV*	*Ascending aorta*
Modal peak velocity:								
Tricuspid valve (TV)	0·18							
Pulmonary valve (PV)	0·33	0·28						
Mitral valve (MV)	0·21	0·30	0·26					
Ascending aorta	0·10	0·07	0·47	0·29				
Descending aorta	0·14	0·06	0·40	0·32	0·50			
Time to peak velocity:								
Pulmonary valve	−0·39	−0·19	−0·25	−0·10	0·06	0·04		
Ascending aorta	−0·38	−0·05	−0·19	−0·34	−0·08	−0·07	0·45	
Descending aorta	−0·30	−0·13	−0·17	−0·16	0·14	0·01	0·54	0·59

SVC, superior vena cava.

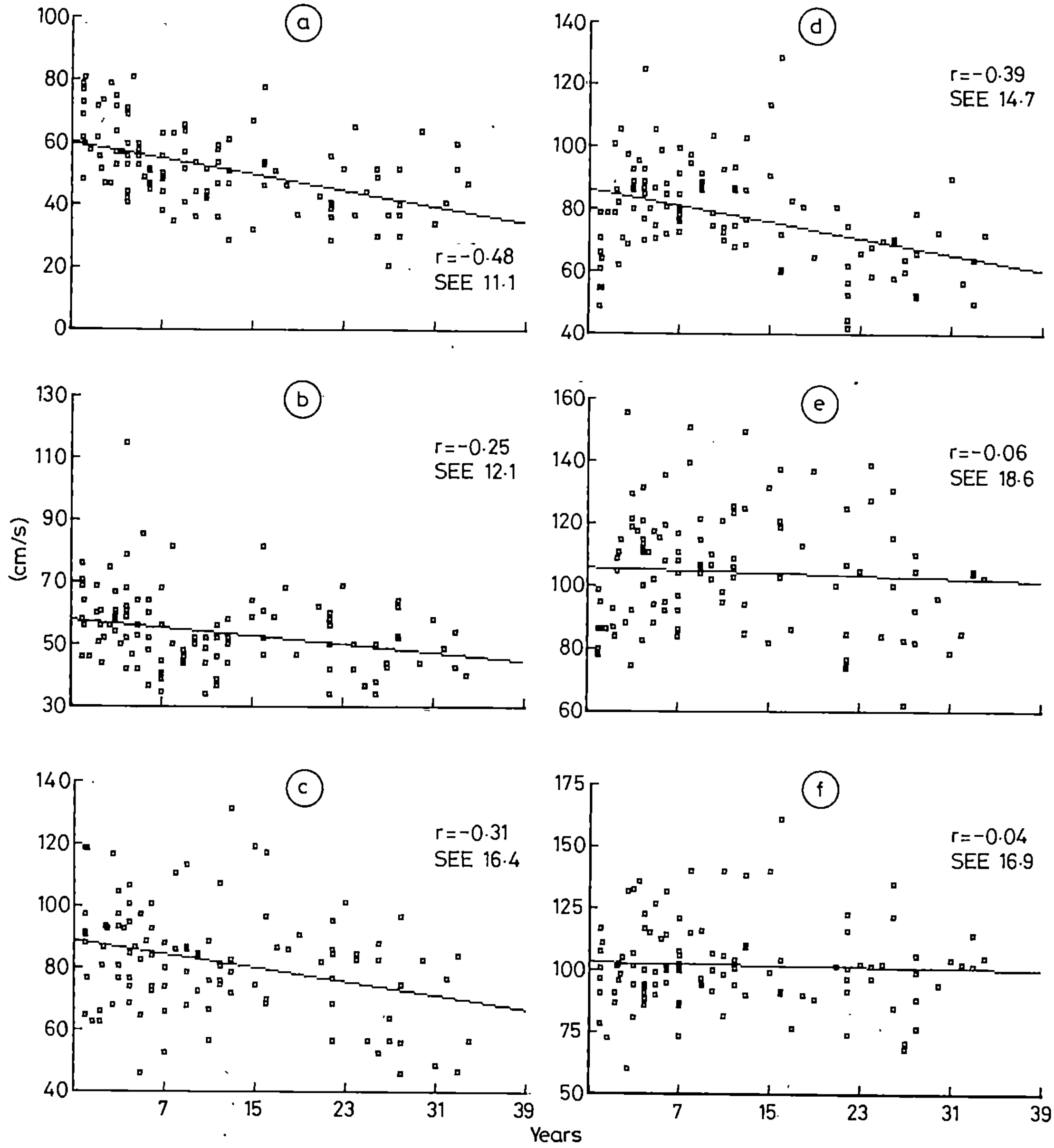

Fig. 2 *Correlation of age (years) with modal peak velocity (cm/s) (a) in the superior vena cava, (b) across the tricuspid valve, (c) in the pulmonary artery, (d) across the mitral valve, (e) in the ascending aorta, and (f) in the descending aorta.*

of the measured variables with age and body surface area. At most sites a statistically significant inverse relation between modal peak velocity and both age and body surface area was found. In the ascending and descending aorta, however, the correlation coefficients with age and body surface area were close to zero.

For time to peak velocity in the pulmonary artery and in the ascending and descending aorta there was a strong positive correlation with both age and body

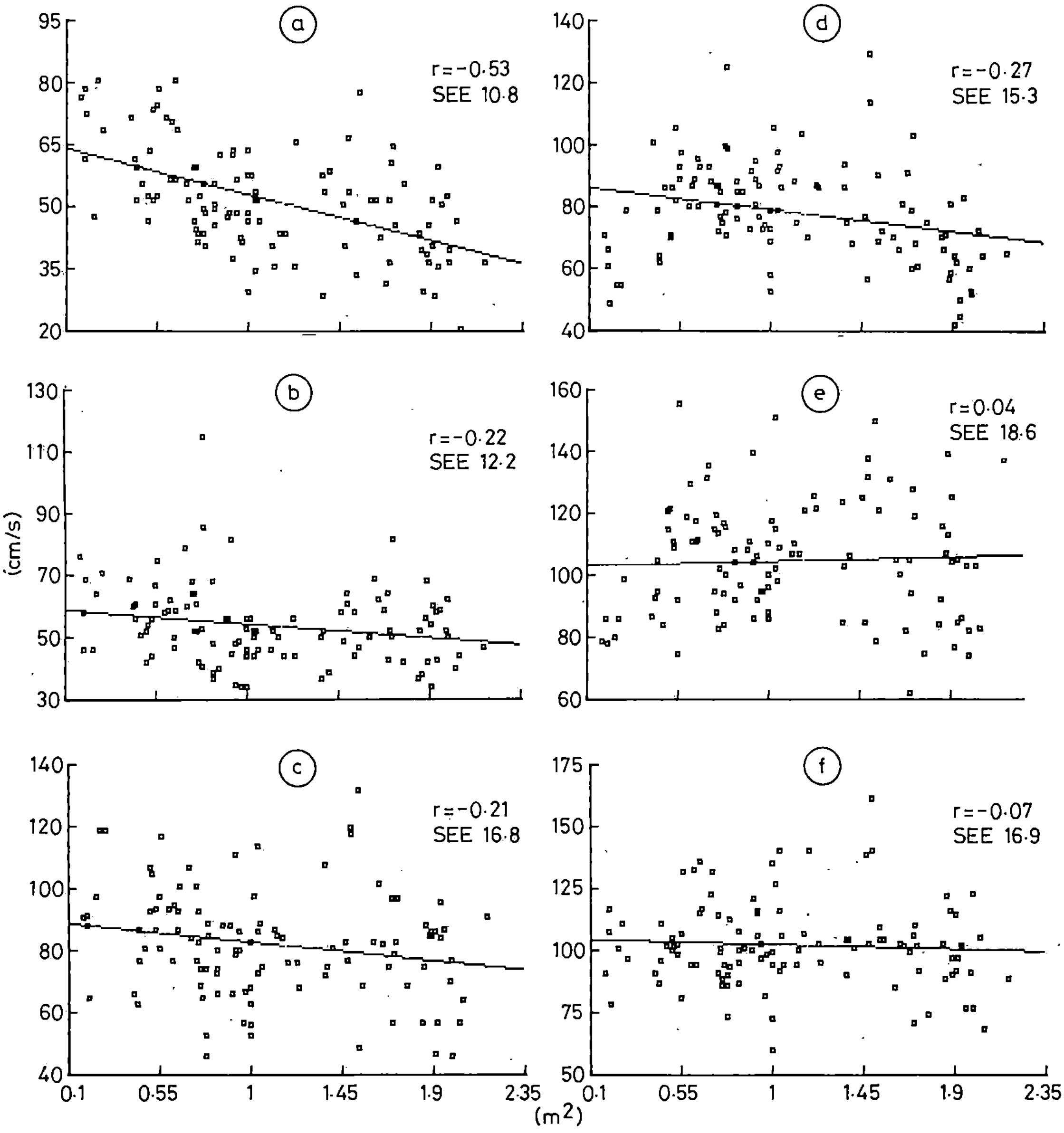

Fig. 3 *Correlation of body surface area (m²) with modal peak velocity (cm/s) (a) in the superior vena cava, (b) across the tricuspid valve, (c) in the pulmonary artery, (d) across the mitral valve, (e) in the ascending aorta, and (f) in the descending aorta.*

surface area. Modal peak velocity generally did not correlate strongly at different sites (Table 3). The correlation of peak velocity in the ascending aorta with that in the descending aorta (Fig. 5) was, however, 0·5 ($p<0·001$).

Discussion

Doppler echocardiography is a useful tool in the investigation of patients with congenital cardiac disease since it allows blood velocity at various cardiac

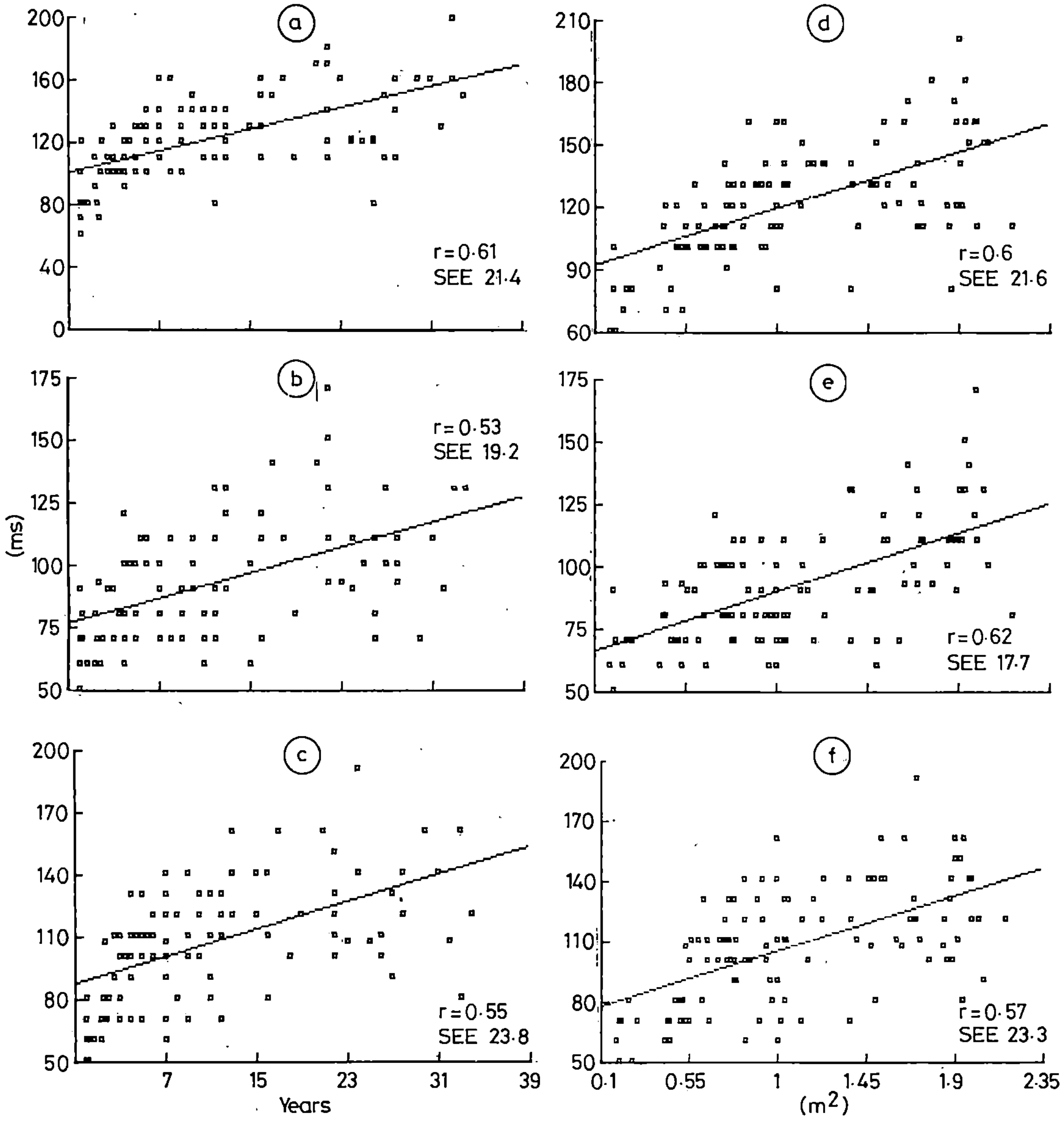

Fig. 4 *Correlation of age (years) and body surface area (m^2) with time to peak velocity (ms) ((a) and (d)) in the pulmonary artery, ((b) and (e)) in the ascending aorta, and ((c) and (f)) in the descending aorta.*

and vascular sites to be measured non-invasively. Velocity measurement, combined with other measurements, permits a quantitative assessment of blood flow and pressure gradients.[1–3] A detailed knowledge of normal values at clinically useful sites is clearly a prerequisite for interpreting data from patients with abnormal anatomy or haemodynamics.

Previous studies, mainly of adult populations, have reported normal values from a limited number of sites,[4–6] some using the continuous wave ultrasound

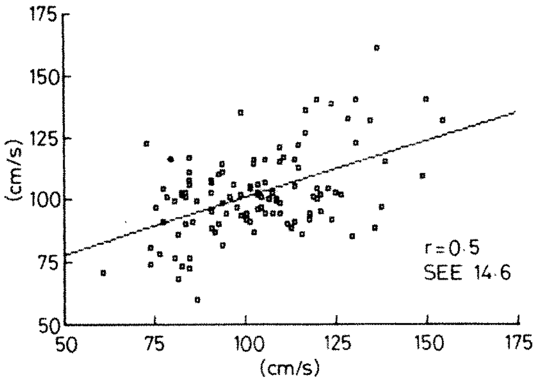

Fig. 5 *Correlation of modal peak velocity (cm/s) in the ascending aorta (vertical axis) with that in the descending aorta (horizontal axis).*

technique. In an earlier study of children by Grenadier and colleagues alignment of the ultrasound beam with blood flow in the third (elevational) plane was not confirmed[5]; thus the reported velocities may have underestimated true velocity. Our results confirm this for some sites.

PROBLEM OF ANGLE CORRECTION

Velocity (V) is calculated from the formula: V=(C dF)/(2F cos theta) where F is the emitted signal frequency, C the velocity of ultrasound in soft tissue, dF the frequency shift, and theta the intercept angle of the ultrasound beam with the direction of blood flow. Accurate measurement of the intercept angle in three planes is impossible with current Doppler instruments. If, however, theta is <20° cosine theta is ≥0·94 and the recorded velocity is correct to within 6% of true velocity. Alignment of the ultrasound beam with flow by the method described should therefore permit a reasonably accurate measurement of maximum velocity without using a potentially inaccurate correction for the intercept angle.

USE OF MODAL PEAK VELOCITY

By definition the modal velocity is that velocity at which most of the blood cells within the sample volume are travelling at any moment in time. On the spectral display it appears as the densest area of the waveform (Fig. 1). During the acceleration phase, virtually all the cells in the sample volume are moving in the same direction at the same velocity and the waveform is a narrow line. At peak velocity there is some broadening of the waveform, although with accurate alignment with blood flow this rarely exceeds a velocity range of >25 cm/s. The peak velocity at the outer edge of the Doppler waveform is a point which, in practice, we have found more difficult to identify precisely, and in our experience modal peak velocity is a more reproducible point from which to make measurements. Although range adjustment will broaden or narrow the spectral display, the value of peak modal velocity will be unchanged.

With the exception of the abdominal aorta, imaged from the subcostal position, the methods we used allowed good alignment with flow at all sites. Modal peak velocity in the abdominal aorta had the widest range and highest standard deviation of any measurement in this study. This variability and the poor correlation between descending and abdominal aortic velocities probably resulted from an inadequate estimate of the spatial intercept angle between the ultrasound beam and blood flow in the abdominal aorta rather than any true difference in modal peak velocity between these two sites. Since the large intercept angle was necessary even small errors in estimation of this angle could make a considerable difference in the calculated velocity. The results suggest that using this method a difference in velocity between these two points could not be regarded as satisfactory evidence of aortic coarctation.

Although at most sites the modal peak velocities recorded in this study are similar to previously reported values[4–6] some points of difference emerge. Not all authors have, however, specified the point from which the measurements were made, and some of these differences may be due to differences in measurement technique. Our mean values for modal peak velocity are close to those of Grenadier *et al*[5] measured using the same method, but the range of values—particularly in the pulmonary artery and at the mitral inlet—are much wider in the present study. Some individuals attained modal peak velocities of approximately 130 cm/s at these sites compared with values of 90–105 cm/s in the study of Grenadier. At these two sites our highest values are more in accord with those of Hatle and Angelsen recorded using a combination of the pulsed and continuous wave Doppler techniques.[3] Nevertheless, Hatle and Angelsen[3] recorded maximal velocities in the aorta far in excess of ours for reasons which we cannot explain. At this site our values are much closer to those of Mowat *et al*.[6]

Within the age range of the subjects in this study there was no change in aortic modal peak velocity with increasing age (Fig. 2c), a finding in keeping with the observations of Light in 120 children aged from 1 to 12 years.[7] In a study of an older population maximal aortic velocity was found to decline with age.[6]

Mahan *et al* found an inverse relation between pulmonary artery acceleration time (time to peak velocity) and pulmonary artery pressure measured at cardiac catheterisation.[8] In the present study pulmonary artery acceleration time is shown to be directly related to age (Fig. 4a), the lowest value of 55 ms occurring in the youngest subject aged 2 weeks. In view of the findings of Mahan *et al*[8] this short time to peak velocity might be attributed to the persistence of a relatively high pulmonary vasomotor tone in these youngest subjects, with some increase in pulmonary artery pressure. No observations are, however, available to confirm this, and at present acceleration times in this age group should be interpreted with caution.

Measurement of modal peak velocity was easy for the ascending aorta but more difficult for the descending aorta. The best alignment with flow is achieved at the junction of the transverse and descending aorta. Nevertheless, an appreciable degree of spectral broadening occurs in this location because cells within the sample volume are changing direction. None the less, ranges for ascending and descending aortic velocity are similar. Furthermore, our results show little velocity change at either site over the age range studied. Time to peak velocity in the ascending and descending aorta lengthened with age.

In accord with previous findings[4 5] modal peak velocity across the mitral valve exceeded that across the tricuspid valve (mean 53 (range 33–81) cm/s for the tricuspid and mean 81 (range 44–128) cm/s for the mitral valve). Superior vena caval velocity varied considerably with respiratory excursion and with increased intra-abdominal tension such as occurs with crying or upper respiratory tract obstruction. In this study all superior vena caval measurements were made with the subject at rest and breathing quietly. If any conclusion is to be drawn from a superior vena caval velocity pattern the above factors must be taken into account. An example of the use of normal superior vana caval velocities occurred during our study when we had the opportunity to examine two infants with total anomalous pulmonary venous connexion of the supracardiac type in whom the ascending pulmonary vein connected to the innominate vein. In these children superior vena caval blood velocity was increased at rest.

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Br Heart J 1985; 53: 459–61

Case reports

Surgery for anomalous origin of the right coronary artery

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SUMMARY In a young man presenting with an episode of syncope and ventricular tachycardia but with no chest pain the right coronary artery was found to originate from the left aortic sinus of Valsalva. After a coronary artery bypass graft he was able to return to full activity.

Origin of the right coronary artery from the left aortic sinus of Valsalva is a rare anomaly. It has not shared the sinister reputation of the corresponding abnormality of the left coronary artery (origin from the anterior aortic sinus). We report its association with syncope and ventricular tachycardia in a patient who had prolonged remission of symptoms after coronary artery bypass grafting.

Case report

A 29 year old computer manager was admitted to hospital in July 1980 after an episode of syncope while playing touch football. He had no history of cardiac disease, was a non-smoker, and had been engaged in regular athletic activity, running up to 70 km a week. On arrival he was pale, dyspnoeic, and sweaty. He was in sinus rhythm with frequent ventricular extrasystoles, his blood pressure was 110/70 mm Hg, and there was a fourth heart sound. An electrocardiogram showed T wave inversion in leads III, aVF, and V1–4, which deepened in V3–4 over the next day. Serum creatine phosphokinase activity was slightly increased (278 U/l, normal range 20–120 U/l). He was discharged taking quinidine and referred for further evaluation.

An echocardiogram was normal. Exercise testing to beyond stage IV (Bruce protocol[1]) provoked frequent ventricular extrasystoles and short runs of ventricular tachycardia. A thallium scan after exercise showed that peak counts over the posterior wall were 30% greater than those over the basal septum. Coronary angiography showed a normal left system. The right coronary artery arose from the left coronary sinus and passed between the aorta and right ventricular outflow tract before taking its normal course to become the posterior descending artery. The abnormal portion appeared to be narrowed between the great arteries (Figure). The left ventriculogram was normal.

Surgery was advised, and at operation (February 1981) the arteriographic findings were confirmed. A single saphenous vein graft was inserted from the aorta to the right coronary artery as it emerged from behind the pulmonary artery.

He had several episodes of ventricular tachycardia in the month after surgery and was treated for six months with quinidine and disopyramide. These drugs were then withdrawn with no recurrence of his symptoms. Five months after operation he was able to exercise on a treadmill to a peak speed of 10 kph with a grade of 20% with only infrequent ventricular extrasystoles. He remained well and returned to full activity. In September 1982 he competed in a "half marathon," running within six minutes of the course record, and in May 1984 was running up to 80 km a week and competing in races of up to 20 km. A 24 hour (Holter) electrocardiogram showed resting bradycardia with frequent ventricular extrasystoles which became less frequent with exercise and during another stress test.

Discussion

Almost certainly our patient experienced some form

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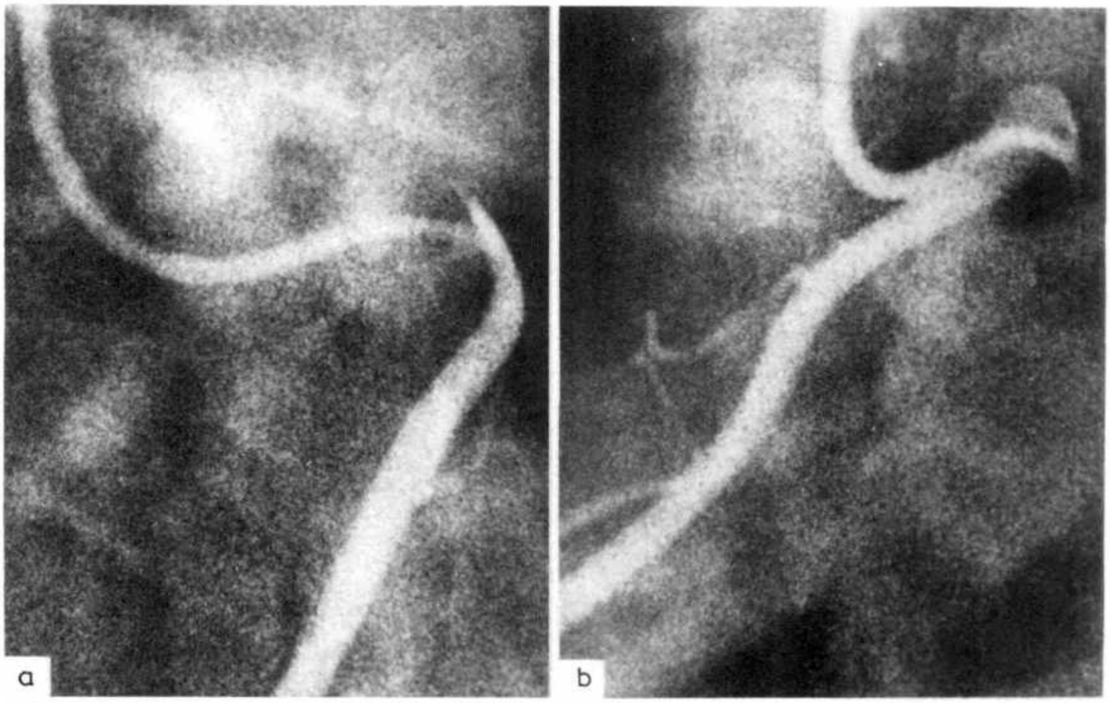

Figure *Right coronary arteriograms in (a) left and (b) right anterior oblique projections showing proximal portion of vessel apparently compressed between aorta and pulmonary artery.*

of cardiovascular event at the time he presented, and given that we subsequently documented exercise related ventricular tachycardia we believe that this was probably an arrhythmia. He had no chest pain, but the T wave changes and fourth heart sound may have been evidence of ischaemia, although the increase in the serum creatine phosphokinase activity might be attributed to release from skeletal muscle because of his exertion, and the thallium scan did not show an exercise related perfusion defect in the distribution of the right coronary artery. Although at the time we were aware of reports attributing ventricular arrhythmias and death to anomalous origin of the left coronary artery from the anterior sinus of Valsalva,[2-4] the corresponding abnormality of the right coronary artery was reported to be without clinical importance, with only isolated instances of associated morbidity.[3 5 6] Nevertheless, there appeared to be no other explanation in this previously very fit young man. We were persuaded by the evident deformity of the proximal right coronary artery that the potential for ischaemia was present. In the circumstances we considered it appropriate to offer him a single graft to the right coronary artery, and although he required treatment for a time after surgery he is apparently no longer at risk from exercise related ventricular tachycardia.

Origin of the right coronary artery from the left sinus of Valsalva is a rare anomaly. In two unselected postmortem studies the incidence was reported as 0·6%[7] and 0·26%,[8] while in angiographic series[5 9] it was less than 0·2%. Origin of the left coronary artery from the anterior aortic sinus is commoner and has been well recognised to cause exercise related arrhythmias and sudden death in young men.[2-4] Before 1980, however, anomalous origin of the right coronary artery was regarded as generally benign[2 4] with only a few reported cases of associated chest pain or arrhythmias.[3 5] In that year Benge *et al* described heart block and posterior wall infarction in a young man with anomalous origin of the right coronary artery from the left aortic sinus,[6] and Roberts *et al* subsequently reported the necropsy findings in 10 patients, in three of whom death was sudden and related to exertion.[10]

The mechanisms that have been postulated include compression of the proximal portion of the coronary artery as it passes between the aorta and right ventricular outflow tract and stretching or distortion of the ostium. Although the latter might seem more plausible, given that the pulmonary artery is more readily compressed than a vessel perfused at systemic pressure, the proximal right coronary artery in our case and in those described by Bloomfield *et al*[11] and

Keren *et al*[12] appeared to be narrowed for some little distance beyond the ostium.

There have been several published reports of surgery for this anomaly.[11 13] One describes a young man with angina, ventricular fibrillation, and inferior infarction, in whom studies at operation showed that diminished coronary reserve in the distribution of the right coronary artery was corrected by a graft. Our patient is the first of whom we are aware who has had vein grafting for this condition and in whom a long period of subsequent good health argues for a successful result.

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Use of amiodarone and digoxin specific Fab antibodies in digoxin overdosage

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SUMMARY A 61 year old man with mild aortic stenosis and chronic depression took 12·5 mg digoxin in a suicide attempt. Ventricular tachycardia and fibrillation were resistant to lignocaine and to phenytoin but responded to intravenous amiodarone, with restoration of pacing. Because of persistent hyperkalaemia he was also treated with Fab fragments of digoxin specific antibody, which bound most of the ingested digoxin.

It is suggested that the treatment of choice in severe digoxin poisoning is amiodarone for ventricular arrhythmias followed by pacing if necessary and the use of Fab antibody fragments if hyperkalaemia persists.

Digoxin overdosage is an infrequent but serious medical emergency, characterised by arrhythmias, hyperkalaemia, and resistance to pacing. The overall mortality is about 20%,[1-3] very high serum digoxin concentrations usually being associated with a fatal outcome.[4-7] The use of Fab fragments of digoxin specific antibody to reverse toxicity has been described recently.[8-10] In addition, amiodarone may be an effective drug for controlling ventricular arrhythmias secondary to digoxin overdosage.[11] We report a case of severe digoxin poisoning in which, for the first time, both methods of treatment were used.

Case report

A 61 year old man with a long history of depressive illness requiring previous inpatient care and electroconvulsive therapy received maintenance treatment with amitriptyline. In June 1983 he developed breathlessness and palpitation and was investigated by another hospital. An echocardiogram showed mild aortic stenosis, and 24 hour electrocardiographic monitoring showed sinus rhythm with occasional ventricular extrasystoles. Treatment was started with digoxin 0·25 mg daily and the amitriptyline withdrawn. After this he became more depressed. In November 1983 he attempted suicide by taking 50 tablets of 0·25 mg digoxin because he understood that "they would slow the heart down." One hour later no effect was apparent so he incised both radial arteries. The bleeding soon stopped, and he gave up his suicide attempt.

On arrival at our casualty department four hours after ingestion of the tablets he was pale but alert with no nausea. An electrocardiogram showed a PR interval of 240 ms with widespread ST segment depression. Haemoglobin concentration was 8 g/dl, serum potassium concentration 4·7 mmol/l, and serum digoxin concentration 11 μg/l. Shortly after admission, he developed ventricular tachycardia and fibrillation alternating with periods of asystole requiring 13 DC cardioversions despite the intravenous administration of lignocaine 100 mg on two occasions and of phenytoin 250 mg. During insertion of a temporary transvenous pacing wire the unstable rhythm continued and required a further 36 DC cardioversions. Figure 1 shows the rhythms recorded at this time: ventricular tachycardia, ventricular fibrillation, asystole with artefacts due to cardiac compression, and failure of pacing to capture despite maximum output (12 V).

Seven hours after ingestion of the tablets amiodarone 150 mg was given intravenously over five minutes. An electrocardiogram at this time showed restoration of pacing capture (threshold 1·3 V) and finally a regular junctional rhythm accompanied by good cardiac output (Fig. 1). A further intravenous dose of amiodarone was given (total 5 mg/kg loading dose) followed by an infusion of 900 mg over 24 hours.

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Nine hours after ingestion of the digoxin tablets his cardiac rhythm was stable, but the serum digoxin concentration had risen to 14 μg/l and the serum potassium concentration to 6·8 mmol/l. It was decided to treat him with Fab fragments of digoxin specific antibody, but as there was only one batch of antibody available in the United Kingdom the antibody was not available for use until 18 hours after ingestion of the tablets. A test dose of 2 mg of antibody was given followed 30 minutes later by 600 mg (60 times the amount ingested assuming 80% absorption) contained in 100 ml of 5% dextrose and infused over 15 minutes.

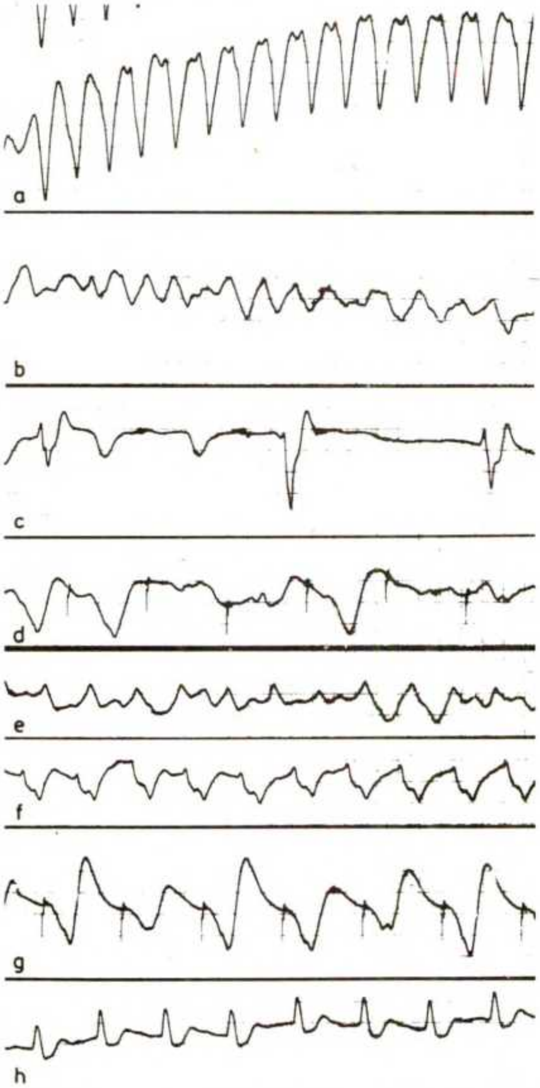

Fig. 1 *Electrocardiogram (lead II) showing rhythms ((a)–(d)) before and ((e)–(h)) after the intravenous administration of amiodarone 150 mg: (a) ventricular tachycardia; (b) ventricular fibrillation; (c) asystole with external cardiac compression; (d) failure of capture of pacing despite maximum output (12 V); (e) ventricular fibrillation at one minute; (f) a regular rhythm at two minutes; (g) capture of pacing (threshold 1·3 V) at three minutes; and (h) a junctional rhythm at four minutes.*

Figure 2 shows the total serum digoxin concentrations measured from the time of ingestion of tablets (0 hours). Within 30 minutes of the administration of the test dose of antibody the total serum digoxin concentration increased 10-fold from 19 to 190 μg/l and the serum potassium concentration fell from 6·2 to 4·0 mmol/l.

Free digoxin was not detected in plasma until 47 hours after ingestion of tablets (2·4 μg/l) and declined thereafter. Urine digoxin concentration was 90–640 μg/l in the six hours before the administration of antibody and rose to a maximum of 2470 μg/l four hours after treatment.

The patient made an uneventful recovery from his overdose and has continued to take oral amiodarone 200 mg daily with satisfactory control of his cardiac symptoms. He was transferred for psychiatric care, treated with mianserin and psychotherapy, and is now back at work.

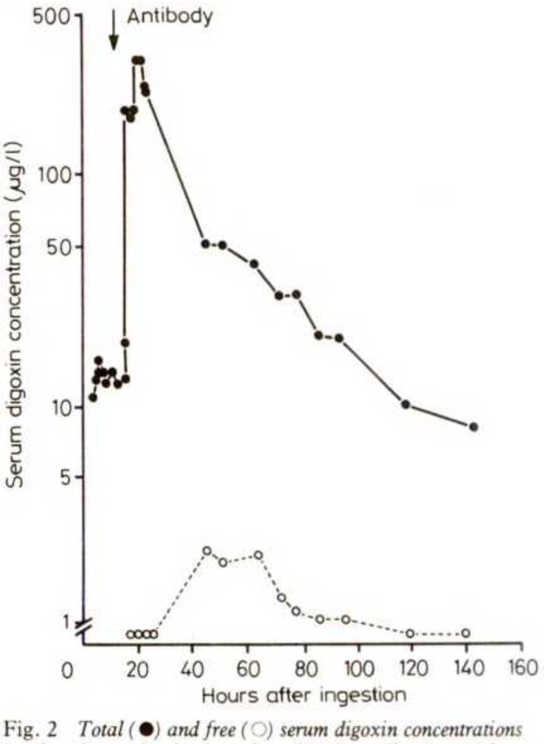

Fig. 2 *Total (●) and free (○) serum digoxin concentrations (μg/l) at intervals after ingestion of 12·5 mg digoxin at 0 hours. Fab digoxin specific antibody 2 mg was given at 18 hours and 600 mg at 18·5 hours after drug ingestion.*

MEASUREMENT OF DIGOXIN CONCENTRATION
Plasma digoxin concentrations were measured by fluorescence polarisation immunoassay (Abbott TDx); the limit of accurate measurement for this method is 0·2 μg/l. Free digoxin was measured after equilibrium dialysis.[8] Total digoxin concentrations, after treatment with antidigoxin antibody fragments, were measured after heating the samples for one hour at 100°C and dilution with digoxin free heparinised human plasma. Plasma amiodarone concentrations were measured using high performance liquid chromatography.[12]

Discussion

The ventricular tachyarrhythmias observed after severe digoxin poisoning may be resistant to treatment. In this case, amiodarone stabilised the cardiac rhythm whereas lignocaine and phenytoin had previously been ineffective, confirming the clinical value of amiodarone in this situation.[11] Control of the ventricular arrhythmias was maintained by infusion of amiodarone, which produced plasma concentrations in the range of 0·6–0·8 mg/l. For comparison, chronic oral treatment with amiodarone 200 mg daily produces plasma concentrations of about 1 mg/l.[13] The reasons for the efficacy of amiodarone in the treatment of digoxin induced ventricular arrhythmias is not clear, but in addition to the antiarrhythmic action of amiodarone it may also displace digoxin from myocardial binding sites.[14] This produces an increase in the plasma concentration of digoxin[15] but may possibly reduce myocardial toxicity. It is interesting to note that in our patient amiodarone also reduced the pacing threshold.

Although amiodarone may stabilise the rhythm disturbances, there remains a large body pool of digoxin to clear. Conventional methods of treatment such as haemodialysis are ineffective because the plasma is constantly replenished from a large tissue compartment. Hyperkalaemia is a sign of severe toxicity[3 4] as it implies failure of the myocardial membrane adenosine triphosphatase pump.[16 17] Although dialysis or glucose/insulin may reduce the serum potassium concentration in some cases, in others the concentration continues to increase and may cause fatal arrhythmias. For this reason, it is important to enhance the clearance of digoxin if hyperkalaemia is present. The effectiveness of digoxin specific antibody in clearing digoxin is shown in this and in the other cases reported.[8-10]

We suggest that the treatment of choice for severe digoxin poisoning should be intravenous amiodarone for life threatening ventricular arrhythmias followed by pacing if bradycardia is evident and the use of digoxin specific antibodies if hyperkalaemia is present.

We thank the Wellcome Foundation for supplies of antibody and Mrs Bowman and the British Red Cross Society for transporting the antibody.

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Coronary sinus type atrial septal defect in a child with pulmonary atresia and Ebstein's anomaly

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SUMMARY At birth an infant was found to have an unusual series of abnormalities with a coronary sinus type atrial septal defect complicating pulmonary atresia with an intact ventricular septum and Ebstein's anomaly. The functionally important anomalies were diagnosed by echocardiography and cardiac catheterisation. The coronary sinus defect and Ebstein's anomaly were detected only at necropsy. Although only a single case, the features of this heart favour Bull's revised classification of pulmonary atresia.

Communication of the coronary sinus with both atria is a very rare congenital abnormality. We report a case occurring in a female infant with an unusual combination of pulmonary atresia and Ebstein's anomaly of the tricuspid valve. We also review the range of coronary sinus type atrial septal defects found in published reports and discuss problems in the classification of pulmonary atresia.

Case report

A girl weighing 4·6 kg was born at the maternity unit at this hospital. Her mother, aged 30 years, had had an uneventful pregnancy and labour was spontaneous at 40 weeks' gestation. Soon after delivery the infant became deeply cyanosed on crying. Examination showed a loud pansystolic murmur down the left sternal edge. Her arterial oxygen pressure (PO_2) was 5·2 kPa and remained unaltered in 95% oxygen. She was transferred to the Hospital for Sick Children, Great Ormond Street, London, where cardiac catheterisation and cross sectional echocardiography were performed. These showed complete atresia of the pulmonary valve with an intact ventricular septum, an atrial septal defect, right ventricular hypertrophy, a small tricuspid valve, and persistent ductus arteriosus. The following day she underwent surgery and had a Blalock-Taussig shunt sutured between the right pulmonary artery and the brachiocephalic artery; her subclavian artery was deemed too small to permit this more usual site of anastomosis to be used.

She had an eventful postoperative course complicated by a right diaphragmatic palsy, empyema, prolonged artificial ventilation, and pneumothorax. She died at 13 weeks old after a cardiac arrest.

NECROPSY FINDINGS

The heart was enlarged. A fenestrated ostium secundum type atrial septal defect was found. Another communication between the atria was present at the site of the coronary sinus. A probe could be guided into both atria and into the coronary sinus through this defect (Fig. 1a). The coronary sinus itself was dilated. No left superior vena cava was present. The right atrium was dilated. The tricuspid valve was displaced apically by about 1 cm from the annulus fibrosus at the septal leaflet. The anterior leaflet was not as severely affected. The valve leaflets were thickened and attached to diminutive chordae and papillary muscles. The valve orifice was restrictive with a diameter of only 0·4 cm. The endocardial surface between the valve orifice and the annulus had an "atrialised" appearance. The septal area of atrialised ventricle contained a blind ending pit where the fibrous tissue adherent to the ventricular muscle swept into the origin of the pulmonary infundibulum (Fig. 1b). The right ventricular cavity itself was very small and the trabecular portion virtually obliterated. Several dilated vascular channels were found in the right ventricular wall. One of these could be traced to the cavity of the right ventricle, although no communication with the coronary arteries could be found. The wall of the right ventricle was hypertrophied (1·4 cm thick) and had a fibrous texture. A thin tortuous

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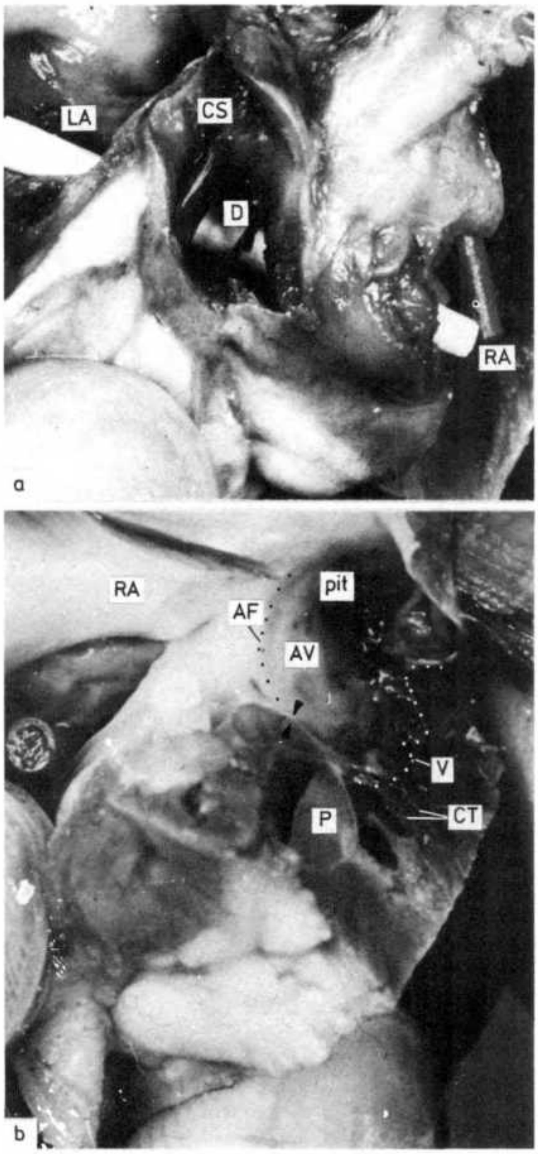


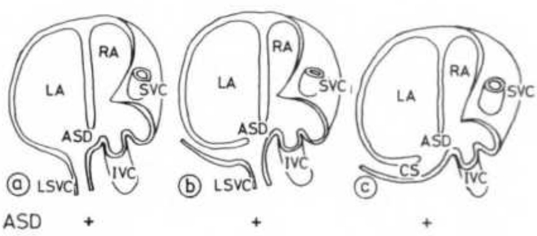
Fig. 1 *(a) Necropsy specimen showing the opened coronary sinus (CS) viewed across the atrial septum. The white probe passed easily from the right atrium (RA) to the left atrium (LA) along the coronary sinus and is visible through the defect (D) in the anterior wall of the sinus. (b) Necropsy specimen showing Ebstein's anomaly of the tricuspid valve. The lumen of the valve (V) is displaced apically. Leaflet material is adherent to the myocardium covering the atrialised ventricle (AV) between the annulus fibrosus (AF) and the valve orifice and is visible as a thin line between the two arrow heads. A blind ending pit is formed by leaflet material lining the origin of the pulmonary infundibulum. Diminutive chordae tendineae (CT) and papillary muscles (P) are present.*

pulmonary infundibulum ended 1 mm below the pulmonary valve. The valve itself was atretic with fusion along the lines of cusp apposition to produce a triradiate raphe appearance. The left sided structures appeared relatively normal except for moderate left ventricular hypertrophy (1·1 cm thick) and dilatation of the aortic root. The coronary arteries and coronary ostia were normal. The ductus arteriosus was patent.

Microscopical examination of the heart showed an endocardial fibroelastosis of the right ventricle but not the left. Dilated vascular channels were present in the right ventricular wall draining the cavity of the ventricle. The myocardial cells of the right ventricle were thin and attenuated, while other areas showed cells with unusually large nuclei perhaps representing a response to the raised intraventricular pressure. The right coronary arterial system showed pronounced fibrointimal proliferation, probably reflecting increased pressure in the arteries.

Discussion

This patient's heart presented a very rare combination of individually rare abnormalities. Mantini and coworkers have comprehensively described the range of anomalies affecting the coronary sinus.[1] Communication of the atria via the coronary sinus has been reviewed by Cohle *et al*.[2] They found eight cases in published reports and added one more. Three of these were incidental findings at postmortem examination. Three cases had evidence of functional left to right shunting through the defect. Three cases described by Rose *et al* had evidence of a congenital obstructive lesion in the heart; one had mitral atresia, one tricuspid atresia, and one stenosis of the orifice of the coronary sinus in the right atrium.[3] No cases of this type of anomaly occurring concurrently with another atrial



ASD	+	+	+
CS	–	+	+
LSVC	+	+	–
AF	Absent	Partial	Partial

Fig. 2 *Diagrams showing patterns of atrial septal defects involving the coronary sinus: (a) Raghib et al*[4]*; (b) Rose et al*[3]*; (c) present case, also Cohle et al*[2] *and Mantini et al.*[1] *ASD, atrial septal defect; AF, atriovenous fold; CS, coronary sinus; LSVC, left superior vena cava; SVC, superior vena cava; IVC, inferior vena cava; LA, left atrium; RA, right atrium.*

septal defect were described. Our case is unique, therefore, in having the two forms of atrial septal defect complicating pulmonary atresia together with Ebstein's anomaly.

Another pattern of coronary sinus defect has been described by Raghib *et al*, who found a persistent left superior vena cava associated with an absent coronary sinus.[4] These abnormalities probably represent a spectrum of maldevelopment of the left horn of the sinus venosus and left common cardinal vein. The sinus venosus is normally partitioned from the left atrium by the left atriovenous fold. Cohle *et al* point out that failure of development of the atriovenous fold would lead to communication of the coronary sinus with the left atrium and an atrial septal defect at the coronary sinus ostium[2] (Fig. 2).

Pulmonary atresia is usually classified into two types.[5] The morphology of the right ventricle is used as the determinant of the type of lesion present. The type I lesion is associated with a small right ventricular cavity and hypertrophy of its wall. The tricuspid valve is said to be hypoplastic but usually competent. Aberrant intramyocardial sinusoids are often found in the right ventricular wall. These vessels may link the cavity with epicardial branches of the coronary arteries.[6] The type II pattern is found with an incompetent valve and has a normal or dilated right ventricle.

The lesions in this heart present problems in classification. The tricuspid valve in Ebstein's anomaly is usually incompetent. When Ebstein's anomaly has been found with pulmonary atresia usually the type II pattern has been described.[5 7] Zuberbuhler and Anderson, however, showed in their 10 cases of pulmonary atresia with intact ventricular septum and Ebstein's anomaly that when the tricuspid valve was restrictive or dysplastic there was an associated hypoplasia of the right ventricular cavity.[8] Although the right ventricular cavity in this case was deceptively small because of the low set tricuspid orifice, nevertheless the hypertrophy of the wall and the presence of intramyocardial sinusoids suggest that this is a type I lesion in the presence of Ebstein's anomaly.

Bull *et al* have proposed a revised classification of pulmonary atresia with intact ventricular septum which places less emphasis on the competence of the tricuspid valve but more on the diameter of its orifice.[9] Their work showed that the diameter of the tricuspid valve decreased with the severity of the ventricular abnormality as assessed by a "tripartite" analysis of the right ventricular morphology. This scheme of classification would accommodate the abnormalities of this heart better than the previous system. The diminutive tricuspid valve orifice in this heart matched the severe right ventricular hypoplasia with absent trabecular portion.

We thank Dr Ashley King for her help and Mr C Burton for the photography.

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Br Heart J 1985; 53: 468–70

Mesothelioma of the atrioventricular node

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SUMMARY A patient with Mobitz type 2 heart block caused by a mesothelioma of the atrioventricular node died of a subarachnoid haemorrhage at the age of 33 two years after implantation of a permanent pacemaker. Mesothelioma of the atrioventricular node is rare, and reported cases have all been diagnosed post mortem. Mesothelioma of the atrioventricular node should be considered in the differential diagnosis of heart block in children or young adults. This is the first case to be reported in Japan.

Case report

A 31 year old man was admitted to hospital because of poor appetite. On routine physical examination, a grade 2/6 systolic murmur was heard at the left sternal border. No cyanosis was noted. The liver was not palpable. Serum aspartate aminotransferase and alanine aminotransferase activities were 58 U/l and 29 U/l respectively. A liver biopsy showed a cirrhotic pattern, and he was diagnosed as having alcoholic cirrhosis.

At night his heart rate fell to 30 beats/min, and an electrocardiogram showed 2:1 atrioventricular block with a narrow QRS complex (Fig. 1). His bundle electrograms were recorded using standard catheter techniques. The HV interval was normal (30 ms) and the AH interval prolonged (150 ms). The echocardiogram was normal. Four weeks later a permanent pacemaker was implanted. Exactly a year later he was readmitted to hospital because of sudden headache and vomiting. On examination his pulse was 72 beats/min and blood pressure 136/86 mm Hg. He was disorientated and there was no neck stiffness. No other neurological abnormalities were present. Computed tomography was performed immediately after admission and showed high density areas in the frontal lobe, lateral ventricles, and subarachnoid space. During the examination he had an episode of apnoea and became deeply comatose. A carotid angiogram showed an aneurysm of the left anterior cerebral artery, and subarachnoid haemorrhage due to a ruptured aneurysm was diagnosed. The patient underwent mechanical ventilation but died on the ninth day after admission.

NECROPSY FINDINGS

The postmortem examination was performed only 16 minutes after death and confirmed an extensive subarachnoid haemorrhage. A ruptured aneurysm of the left pericallosal artery was found. The brain weighed 1·735 kg, which was compatible with so called "respirator brain." The heart weighed 340 g; there was no abnormality in the epicardium, the endocardium, or the valves. The myocardium showed previous and recent ischaemic changes with patchy fibrosis. The coronary arteries were moderately atherosclerotic. The serial sections of the cardiac conduction system showed a small ill defined tumour approximately 1 cm in diameter in the atrioventricular node. Histological sections of the atrioventricular node area showed a benign tumour, a so called mesothelioma consisting of tubular and cyst like structures of varying sizes and fibrous stroma. The tubular and cyst like structures were lined by either single or multiple layers of cuboidal or squamous epithelial cells (Fig. 2). In the lumens and cysts there was amorphous eosinophilic material, which showed strongly positive results when tested with periodic acid Schiff staining and was weakly positive with alcian blue staining. In some areas the lining cells appeared to be stratified squamous epithelium, but there were no apparent intercellular bridges nor keratin material. In the fibrous stroma there were a few chronic inflammatory cells. There was a moderate degree of fibrosis in the sinoatrial node region.

Discussion

Cardiac tumours are rare, and mesothelioma of the atrioventricular node is a very uncommon cause of congenital heart block and sudden death. It has been

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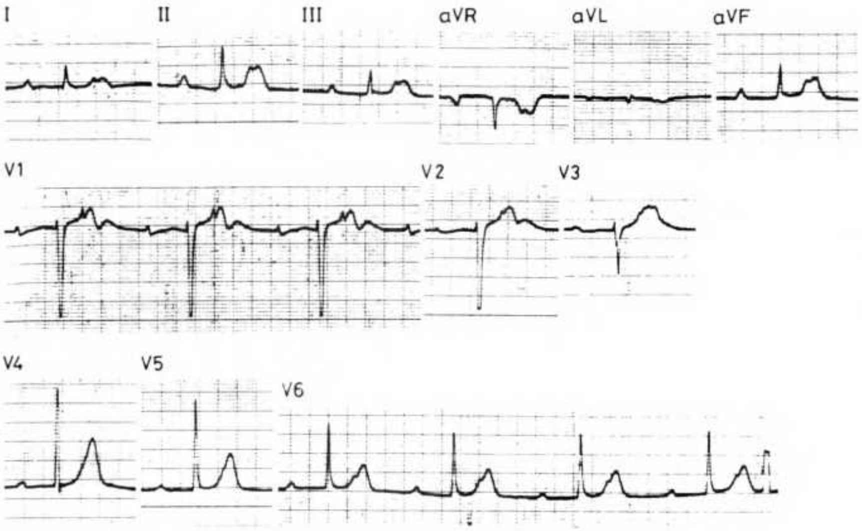

Fig. 1 *Electrocardiogram showing second degree (2:1) atrioventricular block and a ventricular rate of 44 beats/min.*

recognised, however, as "the smallest tumour which causes sudden death."[1] Since Armstrong and Mönckeberg described the first case of this type in 1911 in a 5 year old boy,[2] about 50 cases have been reported.[3-5] The ages of the patients range from eight months' gestation to 86 years with more females affected than males.[6-8] Our case is the first report of a mesothelioma of the atrioventricular node in Japan. Most reported cases have been in patients aged <40 years at the time of death. The cause of sudden death is probably ventricular tachycardia or ventricular fibrillation. Permanent pacemaker implantation did not prevent sudden death in some reported cases.[9-11]

In the present case, a permanent pacemaker was implanted in the right ventricle, but the patient died of subarachnoid haemorrhage. Two similar cases in which the patient died of a cerebrovascular accident have been reported previously[12 13]; nevertheless, the relation between cerebrovascular accident and atrioventricular node mesothelioma is unknown. The Mobitz type 2 atrioventricular block may conceivably have been incidental in this case because moderate coronary atherosclerosis was found at necropsy. Causes of death, other than arrhythmias, have been

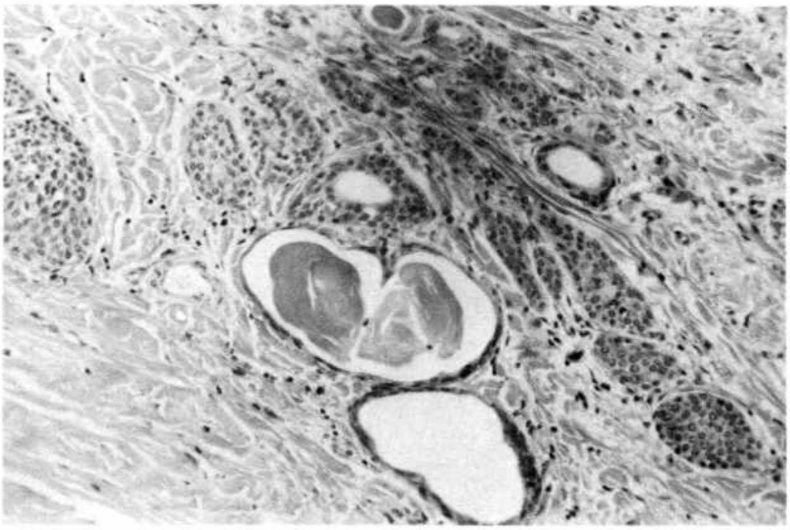

Fig. 2 *Histological appearance of a tumour consisting of cyst like and tubular formations lined by one or several layers of flat or cuboidal mesothelia like cells. In some cysts eosinophilic material is also present. (Haematoxylin and eosin, × 200 original magnification.)*

identified only rarely in patients with this lesion[12–14] and no cases have been diagnosed during life. Nevertheless, Bharati *et al* suggested that it may be diagnosed clinically by selective coronary arteriography.[15] The blood supply of the atrioventricular node and common bundle is derived from the atrioventricular nodal artery, which is a branch of the right coronary artery in nine out of 10 cases. Thus they considered that the lesion could be diagnosed if findings indicating a tumour or an abnormality of the atrioventricular nodal artery were found. We agree with this opinion, but we do not consider that permanent pacemaker implantation is lifesaving because patients usually die of ventricular tachyarrhythmias. Antemortem diagnosis is difficult; nevertheless, a mesothelioma of the atrioventricular node should be considered in the differential diagnosis of heart block in children or young adults.

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Br Heart J 1985; 53: 471–2

Correspondence

Submaximal exercise testing early after myocardial infarction

Sir,
In the paper by Sullivan *et al* (1984; 52: 147–53), I was astonished to read that the ST segment elevation was the only exercise test variable predicting cardiac death in postmyocardial infarction patients. This phenomenon occurs with monotonous regularity in patients with even a minor degree of ST segment elevation in the resting 12 lead electrocardiogram soon after myocardial infarction.[1] To my mind, the only conclusion from this paper is that routine postinfarction stress testing need not be performed in the first place.

The authors' classification of infarcts as transmural and non-transmural on the basis of Q waves ascribes to the 12 lead electrocardiogram the accuracy which the latter simply does not have.[2] Their analysis of cardiac events for the two groups of infarcts showed no significant differences, for reasons that have long ago become obvious.[3]

George Nikolic,
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Australia.

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This letter was shown to the authors, who reply as follows:
Sir,
In his carefully argued criticism of our paper Dr Nikolic cites his own study[1] as evidence that ST segment elevation on exercise occurs with "monotonous regularity" but it actually occurred in only 10% of 50 patients. The finding had been predicted in nine of the 45 tests which were analysed and possibly also in some of those which were excluded because a definite end point was not reached. We were not told the subsequent clinical progress of these patients.

Classification of patients by presence or absence of Q waves is clearly a simplification, but significant differences between these groups have been described.[2] Since ST segment changes alone are highly associated with non-transmural damage[2] it seems reasonable to classify patients in this way when considering the significance of further changes induced by exercise.

The possible prognostic significance of different abnormalities during postinfarction stress testing is still unknown and the place of this procedure in clinical management will only become clear as more series are published.[3] It would be most unusual if all studies on different patient populations produced identical results, and the answers will certainly remain unknown if no more studies are carried out.

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Cardiac transplantation in the United Kingdom

Sir,
The report from the Council of the British Cardiac Society (1984; **52:** 679–82) quotes the Stanford experience and gives the one and five year survival figures as 63% and 39% respectively. Interestingly, these figures are virtually identical with the survival rates for a group of 169 patients with dilated cardiomyopathy (the principal indication for cardiac transplantation) who were treated medically at the Hammersmith Hospital. The one year and five year mortality rates of that group were reported to the British Cardiac Society as 34·7% and 59·4% respectively.[1]

Council's suggestion that cardiac transplantation prolongs life is, on this evidence, difficult to accept, particularly in view of the fact that on an "intention to treat" basis the surgical survival figures would be considerably worse—that is, because of the high early mortality in the sizeable group of clearly very sick patients who did not survive long enough to receive a transplant.

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Reference

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The presentation of symptomatic heart disease in infancy based on 10 years' experience (1973–82)

Sir,
I was interested to read the paper by Scott *et al* (1984; **52:** 248–57) on the Brompton Hospital's experience of the presentation of symptomatic heart disease in infancy. Although the authors recognise that the prevalence rates are unreliable, they make repeated reference to the New England Infant Program. The New England Infant Program is a comprehensive community study, the figures from which must be closer to the true prevalence than those from one centre in London. Further distortion of the figures quoted by the Brompton Hospital arises from the different case selection by the referring paediatrician, who will avoid sending infants to the Brompton if a major non-cardiorespiratory anomaly that may need active concurrent treatment is present.

I would also like to mention that repeated reference is made to the value of joint paediatric cardiology clinics and would like to endorse this statement. I learnt the value of these clinics from the late Dr Ronald Mackeith in 1969 and introduced them to the Brompton Hospital from 1965 onwards.

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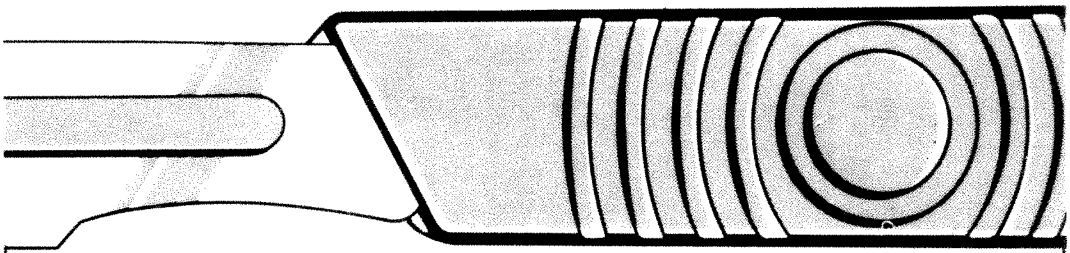
Notices

European Society of Cardiology
A meeting of the European Society of Cardiology (working group on valvular prosthesis) will be held on 11 and 12 October 1985. The subject of this meeting will be "Quantification of valvular regurgitations: appraisal of new techniques." Inquiries about this meeting should be addressed to Professor R Kremer, Cliniques Universitaires de Mont-Godinne, B-5180 Yvoir, Belgium.

British Cardiac Society
The Annual General Meeting for 1985 will take place in Birmingham on 17 and 18 April 1985, and the closing date for receipt of abstracts was 8 January 1985.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.



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May 1985 Vol 53 No 5

British Heart Journal

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A monthly journal of cardiology published in association with the British Cardiac Society

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British Heart Journal

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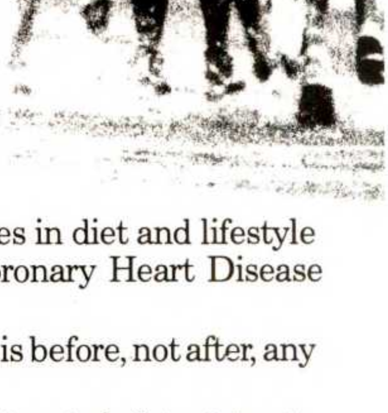

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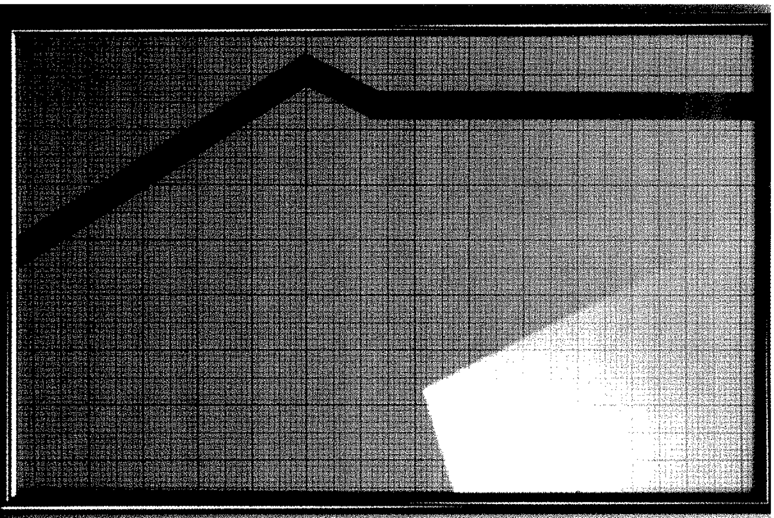

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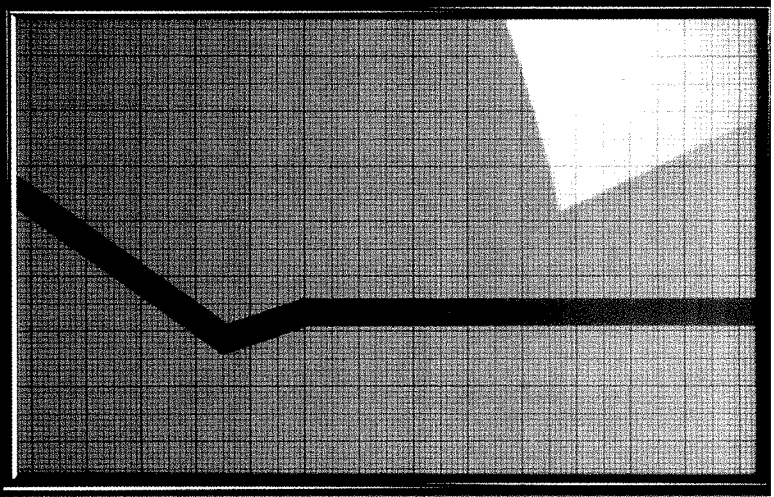

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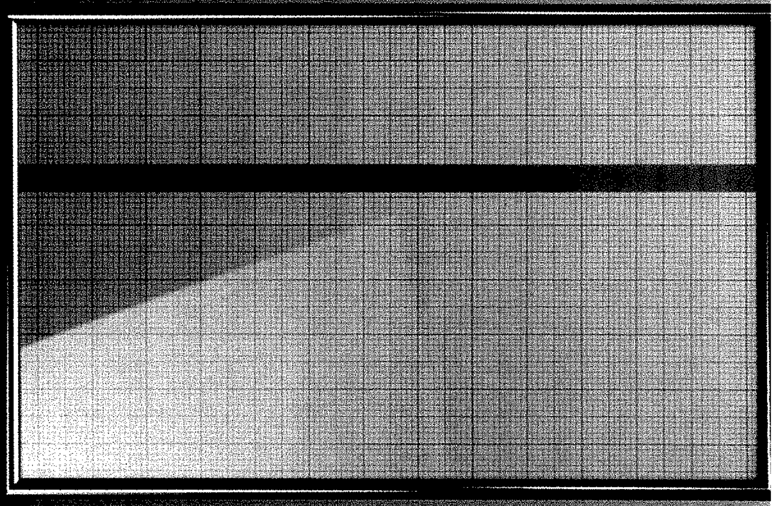

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1. Sharpe, D. N., *et al., Circulation 70,* 1984, **2,** 271.
2. Gomez, H. J., *et al., Journal of Hypertension* (in press).
3. Kjekshus, J. K., *Scandinavian Journal of Urology and Nephrology,* 1984, Suppl. 79, p.115.

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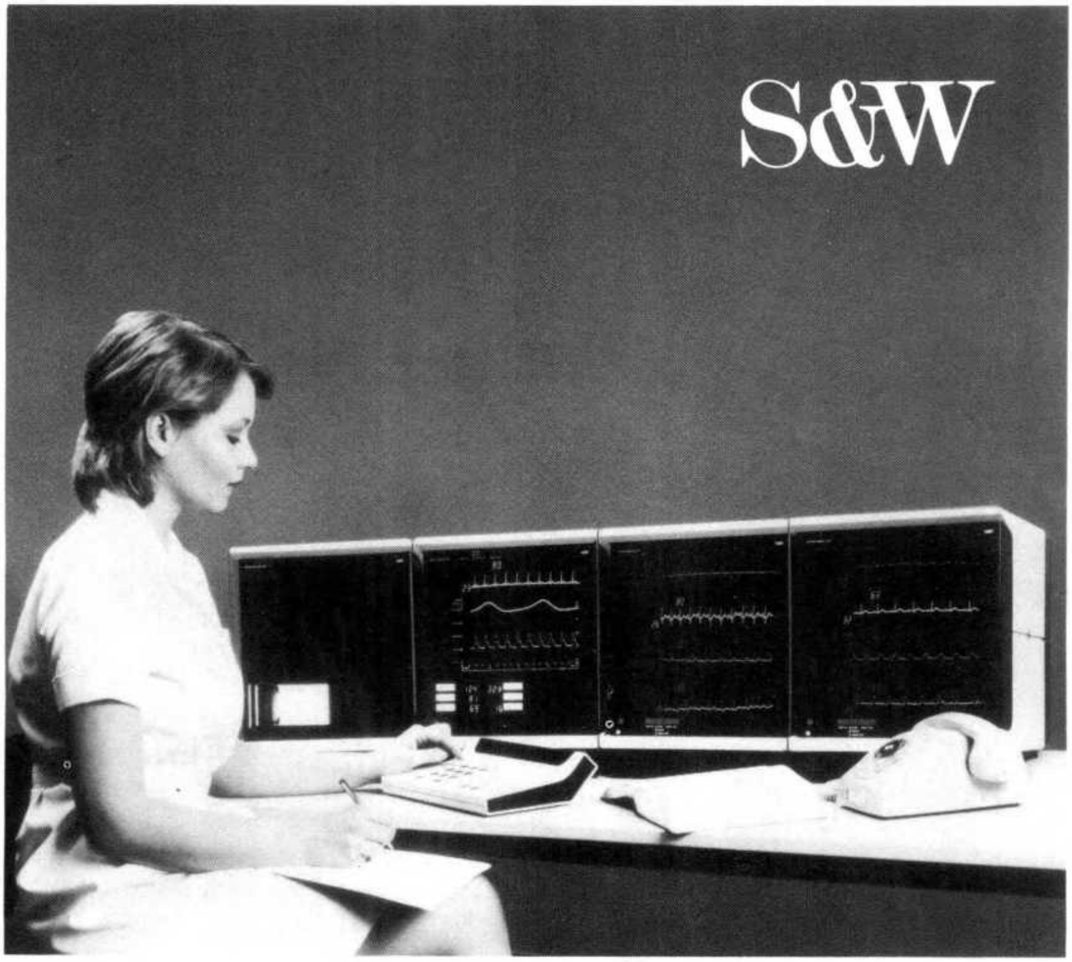

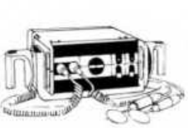
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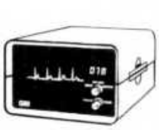
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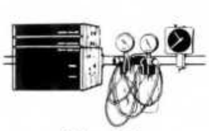
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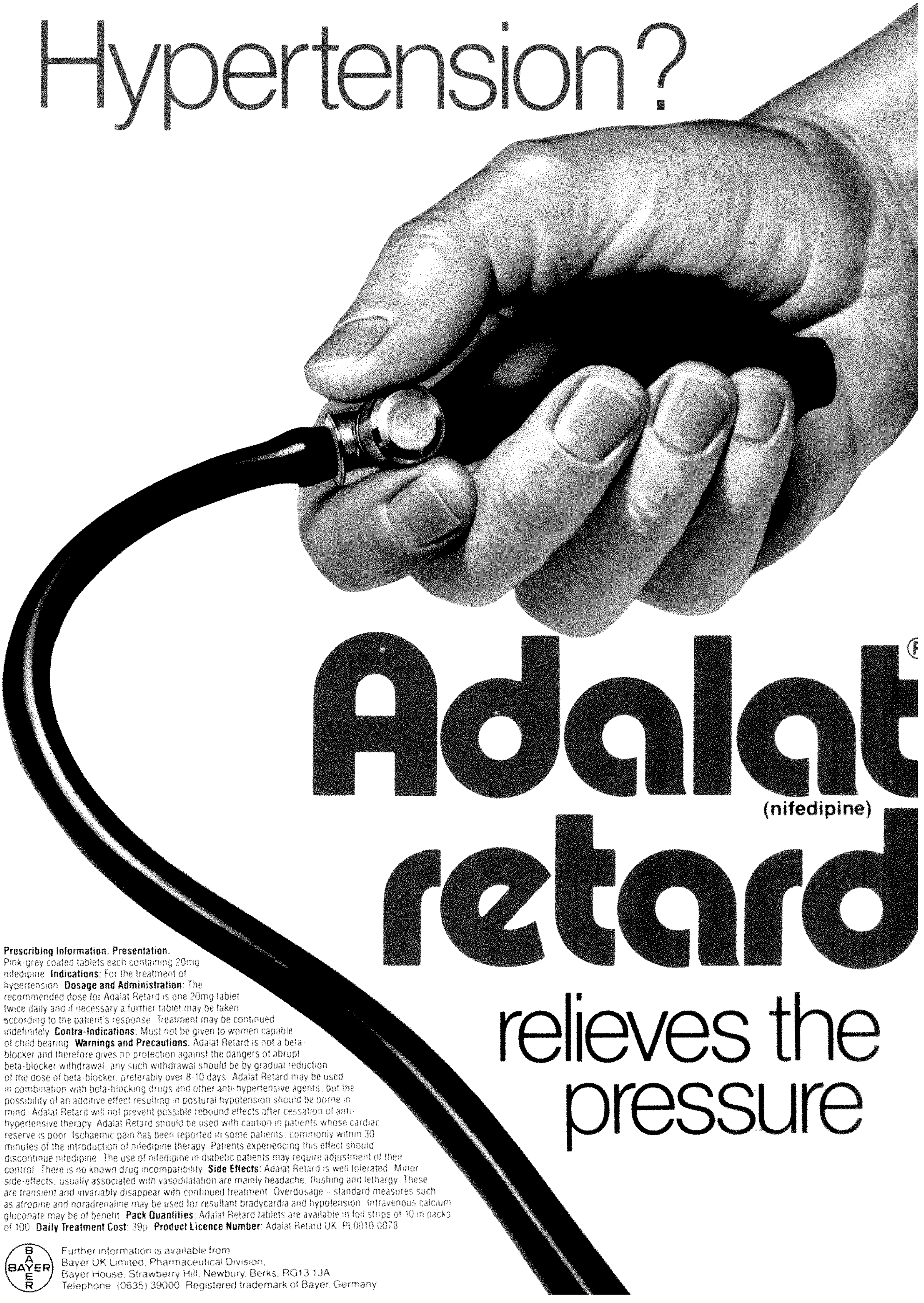

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Br Heart J 1985; **53:** 473–6

Editorial

Thrombosis and ischaemic heart disease

T W MEADE

From the MRC Epidemiology and Medical Care Unit, Northwick Park Hospital, Harrow, Middlesex

Indexes of the abstracts for cardiology meetings usually show considerable preoccupation with the ischaemic myocardium and its electrical difficulties, some concern over atheroma, and very little interest in thrombosis. In terms of pathogenesis and in many respects from the therapeutic standpoint as well, may this not be a case of putting the cart before the horse?

Thrombosis in myocardial infarction and sudden death

The overwhelming dominance of the lipid hypothesis for atheroma has obscured the compelling evidence—some of it of many years standing[1] but some that is more recent[2 3]—that both platelets and the coagulation system also contribute to the lesion. There is much epidemiological evidence[4 5] of some other process besides atherogenesis to account for the clinical manifestations of coronary artery disease. Surprisingly late in the day, and despite the use for many years of the term coronary thrombosis, it became generally accepted that recent thrombus is usually to be found in fatal myocardial infarction and that the first is the precipitating cause of the second. "Recent" should include what may have happened within the preceding days[6] as well as the preceding hours or minutes. Sudden death, though, is not a thrombotic event—or so we have been led to believe over the past 10 or 15 years. One of the reasons for this assertion has been the Seattle study, in which only 16% of those resuscitated after sudden death showed classical signs of myocardial infarction subsequently.[7] Nevertheless, two other studies, much less often cited, gave figures of 39%[8] and 44%.[9] It is hardly surprising that those who have "died suddenly" once should be at high risk of doing so again, an observation which probably tells us more about the consequences than the causes of the initial event. It is, of course, quite possible that the processes involved in a first major episode of ischaemic heart disease may differ from those responsible for recurrences once conducting pathways or myocardium have been compromised. Antithrombotic drugs will be of limited value (which does not mean they will be of no value) in these circumstances compared with those where an initial thrombosis or rethrombosis is the major hazard. Assertions that coronary thrombi are not found in sudden death are also the result of a rather oversimplified citation of published reports. Thus a study quite often said (not by its authors) to have shown no thrombi in sudden death actually established that they were present in about 30% of cases.[10] In any case, an inability readily to detect a thrombus in sudden coronary death does not necessarily mean that thrombosis did not occur. The intense fibrinolytic activity of blood in sudden death (from a variety of causes) has been appreciated for many years so that recent thrombi leading to sudden death may not subsequently be easily identifiable at necropsy.[11] Be that as it may, perhaps the most careful of the necropsy studies has shown intraluminal thrombi in 74% of those in whom sudden cardiac ischaemic death occurred compared with none of those dying suddenly from other causes.[12] Corresponding figures for intraintimal thrombus were 21% and 10·2%. It may be a question of whether it is the blood supply to conducting tissue or to the myocardium that is mainly affected by the evolving thrombus that determines whether sudden death or myocardial infarction occurs. The theoretical desirability of forestalling plaque rupture or haemorrhage as frequent causes of thrombosis is not yet matched by practical methods for doing so. Attention at this stage of pathogenesis therefore inevitably has to focus on modifying the thrombotic process itself.

Modifying the thrombotic process

If, then, there is a major thrombotic element in both myocardial infarction and sudden coronary death, how can it best be prevented? The Dutch Sixty-Plus

Requests for reprints to Dr T W Meade, MRC Epidemiology and Medical Care Unit, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

trial assessed the effects of discontinuing rather than initiating treatment with anticoagulants.[13] None the less, with its striking results in favour of continuation this trial makes a re-evaluation of anticoagulants essential and reopens the question as to which part of the thrombotic process—platelet activity or coagulation—is mainly involved. So far as the secondary prevention of infarction is concerned, anticoagulants may be more effective than aspirin not only in reducing the risk of death[14 15] but, in particular, in forestalling thromboembolic events, including reinfarction, where benefits of 50% or over have been found.[13 16 17] A possible explanation lies in the effects of anticoagulants on the production of thrombin, which is a potent platelet aggregating agent as well as being responsible for the production of fibrin. We do not yet have information about antithrombotic agents in primary prevention where, if both infarction and sudden death are indeed substantially thrombotic, their potential may be very considerable. If so, it is at least arguable—and only the appropriate trials will settle the point—that modifying the capacity for producing thrombin may be more effective in primary prevention than the use of aspirin, which will inhibit neither thrombin induced platelet aggregation nor the production of fibrin. What, on the other hand, should we make of the striking benefit apparently conferred by conventional dose aspirin on those with unstable angina?[18] May it be that the pathogenesis of infarction in unstable angina differs from that after a previous infarction, with platelet activity contributing predominantly in the former case and less in the latter? There is some evidence that may support this view.[19] How, also, does the low dose aspirin hypothesis now stand in the light of the findings of the unstable angina trial?

The haemostatic system

To many, thrombosis seems a purely structural event—mere plumbing, perhaps, compared with what are seen as its more intriguing functional consequences for the conducting system and myocardium. This is to undervalue not only the clinical importance of thrombosis but also the scientific interest provided by the study of the haemostatic system. The processes that lead to the production and removal of fibrin under both physiological and pathological circumstances are among the most complex in the body. In his early account of the coagulation cascade Macfarlane proposed that its intricate and self-amplifying nature is the result of the natural selection of increasingly efficient biological mechanisms for the sudden conversion of fibrinogen to fibrin.[20] The question is whether some stimuli (smoking or obesity, for example) may increase the risk of "haemostasis in the wrong place," to use Macfarlane's shorthand description of thrombosis.[21] Some argue that since clotting factors are mostly present in considerable excess anyway, high concentrations are unlikely to be involved in thrombogenesis. This argument is, however, surely only logical in terms of their physiological function—the control of bleeding. A minimum level of blood pressure is required to ensure an adequate circulation, but there is no dispute that raised levels have undesirable consequences. Why, in principle, should the same not be true of some of the clotting factors? Three examples are worth considering in this light.

Factor VII occupies a key position in the extrinsic system, and, on the cascade model, quite small increases in activity might be expected to have substantial effects on the potential for thrombin production, particularly as the extrinsic system is, at best, poorly counterbalanced by antithrombin activity. It now seems increasingly likely that factor VII activity is an index of coagulability if not also a contributor to the degree of this coagulability.[22] The general epidemiology of factor VII activity is consistent with the hypothesis that high concentrations are of pathogenetic significance—for example, high concentrations are found in oral contraceptive usage, after the menopause, in obesity, in diabetes, and with increasing age. Prospectively, high concentrations are associated with an increased risk of death from ischaemic heart disease.[23] Nor does there have to be any continued polarisation between the lipid and thrombotic hypotheses for ischaemic heart disease so far as factor VII may be involved, since it is also likely that lipids are one of the determinants of factor VII activity.[22]

A second component, already referred to, is thrombin. The presence of fibrin in arterial wall lesions[3] establishes that intravascular thrombin production occurs. The ability to detect and measure thrombin production is limited since its half life is so momentary. Practicable if indirect methods are, however, now available, including the radioimmunoassay of fibrinopeptide A, the initial cleavage product of the thrombin proteolysis of fibrinogen. The use of this assay is beginning to confirm and characterise the crucial role that thrombin may play in the pathogenesis of ischaemic heart disease. Thus, in vitro, an increase in factor VII activity is remarkably closely paralleled by an increase in fibrinopeptide A.[24]

A third component of the coagulation system whose importance is now increasingly recognised is fibrinogen, which has effects other than its obvious involvement in the production of fibrin. It is a cofactor in platelet aggregation[25 26] and increases blood viscosity both in cellular and plasma terms and thus, very probably, the risk of coronary artery disease.[27] At p 483 in this issue Yarnell and his colleagues describe the cross sectional associations between fibrinogen and other indices of ischaemic heart disease risk in their South Wales population. They point out that their results are compatible with the concept of a "hypercoagulable state" whose definition may be improved by the heparin-thrombin clotting time. In due course, prospective data will also be available from the South Wales group. In the three incidence studies that have so far been reported, high concentrations of fibrinogen have been associated with increased risks of ischaemic heart disease, strongly in two from the United Kingdom[23 28] and convincingly though not as strongly as for cerebrovascular disease in a Swedish study.[29] Just how striking this association may be is indicated by the distinct possibility that the fibrinogen concentration has the edge over age[28] in multivariate analyses of the risk of ischaemic heart disease. In view of the several effects that high fibrinogen concentrations may exert, it remains a question of perhaps secondary importance as to whether these concentrations are simply a marker of underlying vessel wall damage or the result of genetic and environmental influences. The development and evaluation of acceptable agents for lowering plasma fibrinogen concentrations are now of considerable importance. Stanozolol is an example, though since it is an anabolic steroid its widespread use is unlikely.

Perhaps because of its particular complexity, the haemostatic system has tempted many to try to work out its contribution to ischaemic heart disease by theory rather than fact. Nowhere has this recently been more apparent than in the low dose aspirin hypothesis for differentially modifying thromboxane and prostacyclin production. The studies that have been undertaken have in general only extended the hypothesis—they have not convincingly confirmed or refuted it. Not only is the "right" dose still undefined but the relevance of thromboxane and prostacyclin to the vessel wall under other than exceptional circumstances is being questioned. But no one knows for certain. The thrombogenic effects of changes in fatty acid intake and metabolism currently run the risk of being decided more on theoretical than experimental grounds, though it is not too late to forestall this. The crucial evidence, usually, will be what happens in man under conditions that are not grossly artificial. As often as not, this means randomised controlled trials. The fact that these may be long and often difficult is a poor argument against doing them.

Conclusions

If there were no atheroma there would be virtually no ischaemic heart disease. To the extent that the prevention of clinical ischaemic heart disease in developed, and developing, communities can realistically be attempted through the prevention or regression of atheroma, further work in this field may be justified. The effects of coronary occlusion on electrical and myocardial function vary from patient to patient, so for this and many other reasons the study of the functional consequences of thrombosis in both pathophysiological and clinical terms must continue. Clearly, appreciating and understanding thrombogenesis is not the whole story. At the same time, there is now a robust hypothesis that thrombogenesis does play a central part in ischaemic heart disease not only as one of the acute or subacute complications of atheroma but also, much more chronically, in the initial development of the atheromatous lesion. It is quite conceivable that the significance of thrombosis as an initiating or aggravating process differs between first and recurrent episodes and that the relative contributions of platelets and fibrin formation vary from one set of circumstances to another. These possibilities and the hints that suggest them are surely additional reasons for not side stepping an issue which, controversial and complex though it may be, needs to be clarified in the interests of both the prevention and management of ischaemic heart disease.

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Provision of services for the diagnosis and treatment of heart disease in England and Wales

Third Report of a Joint Cardiology Committee

ROYAL COLLEGE OF PHYSICIANS OF LONDON AND THE ROYAL COLLEGE OF SURGEONS OF ENGLAND

SUMMARY The principal conclusions of the report are as follows. (1) Cardiology continues to change rapidly. In the five years since the issue of the *Second Report of the Joint Cardiology Committee* in 1980 the specialty has been affected principally by the increase in coronary artery surgery and the increasing importance of non-invasive techniques of diagnosis, particularly echocardiography. (2) The burden of heart disease in Britain shows some decline recently, but this falls short of that which has occurred in other countries. The vital role of the initial assessment of patients to ensure the efficient use of limited resources falls upon physicians and paediatricians in district general hospitals. (3) Each district general hospital should have at least one physician, practising general medicine but having a special expertise and training in cardiology. He should undertake echocardiography, stress testing, ambulatory monitoring, emergency pacing, rehabilitation, and cardiac intensive care, with the necessary facilities and staff. He will also play an important part in the follow up of patients assessed and treated at cardiac centres. (4) Paediatricians should continue to evaluate children with heart disease and their training should include periods at cardiac centres. (5) Cardiac centres currently undertaking invasive investigations and cardiac surgery need to expand to cope with demand. A target figure of 750–1000 coronary artery bypass operations annually is suggested. This implies three or four surgeons and six cardiologists per centre. Other staffing should be based on these figures. Smaller centres are not necessarily non-viable but should be encouraged to expand or merge. (6) Funding should be clarified so that regional contributions to regional services are identified and not lost in district budgets. Expensive capital equipment should be regionally funded whether sited in cardiac centres or district general hospitals. (7) Supraregional centres for the cardiac problems of infants under the age of one year have been identified and should receive supraregional funding. Their staffing and equipment should be appropriate to the exceptional demands of this work. If such a centre is sited within an existing cardiac centre the staff will be additional to those needed for the adult work. Facilities for older children should continue to be provided, as at present, at all cardiac centres. (8) Cardiac transplantation should be funded supraregionally. (9) The medical audit of cardiac work should be supported by the Department of Health and Social Security (DHSS). (10) Research remains a high priority, and cardiac centres should be provided with the facilities, and staff with the contracts and time, to undertake it. (11) A revision of this report is recommended within five years.

The *Second Report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England*, published in 1980,[1] extended and updated the original report of 1968, 12 years earlier. In recommending a further review within the much shorter period of five years, the committee of 1980 recognised not only the continuing change in the specialty of medical and surgical car-

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diology but also the likelihood that the pace of such change would accelerate. Events have borne out this prediction. For example, echocardiography, both in paediatric and adult heart disease, has made huge strides, and the surgery of complex congenital cardiac defects has grown more adventurous. Overshadowing everything, the number of patients being referred for the acknowledged benefits which coronary artery bypass grafting can confer both on symptoms, and prognosis for certain groups, now constitutes a major logistical problem.[2]

The past five years have also seen the advent of coronary angioplasty and intracoronary thrombolysis, with demands on resources and staff as yet undefined. Exercise testing has assumed new dimensions, rehabilitation programmes after infarction have become established, and prehospital coronary care has proved its value. Further off, but approaching, are advanced techniques, the impact of which have yet to be felt, such as nuclear magnetic resonance, laser technology, computerised cardiac tomography, and the prenatal diagnosis and treatment of some congenital lesions.

Since the Second Report there has been a marked reorientation in the concept of providing cardiac services for the population. This has occurred mainly because of the rapid development and proven value of non-invasive diagnostic methods. The principle is established, and widely accepted, that these techniques should be used in initial acceptance and therefore should be available at all district general hospitals, where there should be a physician with special interest and training in these aspects of cardiology. At the same time, because of the success of coronary artery surgery, a large increase has occurred in the work referred to cardiac centres. So far, financial restraints have prevented adequate expansion of either staff or resources, a situation already deplored in the 1980 report, and the senior registrar bottleneck in medical cardiology, though showing some improvement, is still a matter for grave concern.[3] The committee notes, however, that the proposals for supraregional centres, rationalising the provision of cardiac services for infants, advocated in the Second Report, and supported since,[4] are coming to fruition.

The necessity for a third report speaks for itself.

Terminology

A cardiologist is a physician who has received formal training in cardiology, spends the major part of his time practising the specialty, but may also have responsibilities in general medicine.[3] He may work in a district general hospital or in a cardiac centre where invasive investigations and cardiac surgery are carried out.[1]

In practice, there is a spectrum of roles within cardiology. Some cardiologists working primarily in a cardiac centre will have a limited commitment in general medicine, while others at district general hospitals may spend part of their time in a cardiac centre.

The burden of heart disease

Cardiovascular diseases are by far the most important causes of death, particularly premature death, in Britain. Data from the Office of Population Censuses and Surveys show that coronary heart disease is the dominant cause of death in men after the age of 40.[5] In 1978 it accounted for about 40% of all deaths in men aged between 35 and 64 years.[6] While certification of death may not be accurate, the results of a large scale necropsy study in the United States suggest that conclusions based on clinical data do not markedly overestimate the toll; in Rochester, Minnesota, 40% of all deaths in men over a 10 year period were attributed to coronary disease.[7] In women, the mortality in each age bracket corresponds approximately to that of men 10 years younger. In the United States, Canada, Australia, and Finland, deaths from this cause have fallen and there is some suggestion that a similar trend may be starting in Britain.[8 9] If this improvement has resulted from primary preventative measures, and this remains to be shown, we in Britain can draw small comfort; and prevention, even if successful, cannot be expected to bear early fruit.

The morbidity of coronary heart disease is considerable. The prevalence of angina has been reported as 4·8% in men aged between 40 and 64 years,[10–12] a probable underestimate of the true figure in the community since these data were obtained by questionnaire from those still at work. Heart failure, the other principal manifestation, is common. In one study it occurred in 23% of those surviving for one month after myocardial infarction.[13] The economic consequences are serious. The number of work days lost because of coronary heart disease rose between 1969 and 1975; in contrast, in all other conditions it fell. The disease now accounts for over 8% of all certified incapacity in men.[14] A sizeable proportion of hospital resources are committed to its treatment: the most recent report of the Hospital Inpatient Enquiry estimated that it accounted for nearly 150 000 admissions to hospital each year and for the occupancy of 7500 beds at any one time.

Other forms of heart disease remain important causes of death and disability. Though rheumatic heart disease is seen less often, degenerative mitral lesions seem commoner, and calcific aortic valve disease appears as frequently as in the past. Overall, the number of those requiring valve replacement has remained static.

Idiopathic conducting system disease, presenting as bradycardia, syncope, or sudden death, is a continuing problem and one probably insufficiently recognised as a cause of otherwise unexplained confusion, dizziness, fits, faints, and trauma, especially in the elderly,[15] as experience with ambulatory monitoring has shown. It is likely that only a minority of those who could benefit receive pacemaker implantation, and the figure for those so treated per million of population in Britain lags behind those in other European countries.[16]

The incidence of congenital heart disease remains at eight in every 1000 liveborn children and another one or more per thousand will have a congenitally determined arrhythmia. While surgery has transformed the management of many of these abnormalities, its very success has created new and particular diagnostic and therapeutic needs, and these are discussed in more detail below.

Similarly, the reduction in hypertensive heart disease which modern drug treatment has achieved has been purchased at the cost of a sizeable investment in specialist supervision.

Requirements for a cardiac department in a district general hospital

Widening appreciation both on the part of doctors and the public of the advances in medical and surgical treatment outlined above has led to increasing demands in the past five years for specialist services to identify those patients likely to benefit, and the task of selection falls first on the district general hospital. It is in this area of the cardiac services where the most serious deficiencies exist and will intensify if current trends continue. A recent survey has shown that, of 215 health districts in England and Wales, only 152 had a member of staff with special expertise in cardiology,[3] though since then the number has increased slightly. This leaves 12 million of the population without a cardiologist or physician with cardiological training in their own district. Yet with resources at cardiac centres limited, the skilled selection of patients locally is vital. It is, furthermore, with new non-invasive methods of diagnosis now a task transformed. To function effectively the committee considers that every district general hospital should have at least one physician with cardiovascular training on its staff, who, by the nature of his appointment, will also undertake general medicine. Some will have sessions in the cardiac centre. There are other arguments in favour of improving and extending the cardiac services available in district general hospitals—the need for patients to be treated whenever possible close to their homes, the relief from the burden of travel for follow up visits, and the raising of clinical standards—but the overriding argument is for the economic use of the high cost special resources of the cardiac centres engaging in cardiac investigation and surgery. Some health districts have accepted the need and pioneered the way; others have done nothing. The manpower to staff district hospitals already exists in the current cohort of well trained senior registrars in cardiovascular medicine currently frustrated from advancing to consultant rank by scarcity of posts. The cost of the extra equipment required, much of it in any case already available,[3] is not prohibitive.

STAFFING

The committee recommends, therefore, that each district general hospital should have at least one physician with special training in cardiology; larger hospitals might have two. Supporting staff should include at least one registrar, who will probably be in a rotating post and not committed to cardiology as a career.

CARDIAC CARE UNIT

A cardiac care unit should be available in all district general hospitals as well as in cardiac centres. The narrow designation of "coronary care units" should be abandoned as these units will admit patients with many different pathologies for monitoring and treatment. The cardiovascular physician should be in administrative charge, but some physician colleagues will wish to manage their own patients, accepting expert help for special procedures such as pacemaker insertion. A unit should contain six or more beds, depending on local circumstances, with a procedures room and the facilities for the implantation of temporary pacemaker wires. Immediate on site access to image intensification is essential. A unit should be adjacent to but not integrated into an acute medical ward. Close proximity to a general intensive care unit is an alternative arrangement which may be convenient for equipment and staff, but cardiac patients should not be nursed in company with those admitted to such units. Many district general hospitals already have cardiac care units run on these lines.

OTHER FACILITIES

District general hospitals, in addition to routine electrocardiography, should have facilities for exercise testing and for ambulatory monitoring. Echocardiography will be needed. Nuclear cardiology, if available, will increase the diagnostic and research potential. The implantation of permanent pacemakers will usually be undertaken at the nearest cardiac centre but may also be carried out in the district general hospital if the physician concerned has the interest and expertise. Pacemaker follow up clinics, however, should be available in every hospital of this kind. Rehabilitation programmes should be undertaken. All these tasks imply an adequate establishment of properly trained technical staff.

Cardiac centres

SIZE

The role and siting of the existing centres which undertake specialist investigation and cardiac surgery were defined in the Second Report and require no restatement. The Second Report also emphasised the importance of size, however, and this aspect merits reassessment. The potential of a centre is usually limited by its surgical throughput, and this in turn determines the population which can be served, once the number of patients likely to need surgery is known. Facilities for cardiac catheterisation rarely limit the output of a centre. The present estimates for coronary artery disease are that 400–500 coronary artery bypass operations or angioplasties per million of the population will be needed per year.[2] The precise role of angioplasty has yet to be defined but appears to be increasing. In addition, it is estimated that 100 per million require valve surgery and 40 per million paediatric surgery. At the same time, staff and facilities have to be economically employed to achieve maximum output with maximum efficiency. In 1980 the recommendation was that, with at least three surgeons in every unit, 600 bypass operations should be performed annually, since surgeons undertaking less than 200 operations a year often had results with higher than average mortalities. In indicating this figure, however, the committee of the time recognised that some centres nevertheless achieved good results with lower numbers and, while urging such centres to expand or merge, did not wish to insist on over-rigid guidelines. This remains its position, but in the past five years most cardiac centres have carried out increasing numbers of operations,[2] much of the increase being coronary artery bypass procedures, though valve surgery still accounts for a significant proportion of the total. Thus, given the prediction that 400–500 bypass operations per million of the population are currently necessary annually for the relief of intractable angina and in response to the accepted prognostic indications, the committee now recommends a target for each centre of 750–1000 operations a year.

STAFFING

It follows from the previous paragraph that each centre should be staffed by three, and preferably four, consultant cardiac surgeons. The Second Report emphasised the need to allow for the demands of emergency work, leave, sickness, teaching, and research, as well as for clinical duties. In some centres, in which thoracic surgery is also undertaken by surgeons primarily involved in cardiac work, an additional surgeon may be necessary. The role of cardiologists has altered to some extent since the previous report, with a greater emphasis on coronary arteriography and, increasingly, on invasive interventions such as angioplasty, balanced by an expansion of non-invasive investigations such as echocardiography. Subspecialisation in such fields as electrophysiology, pacing, and nuclear cardiology continues. The committee repeats its earlier recommendation that the equivalent of six whole time consultant cardiologists is desirable, the exact number depending on the degree of involvement of radiologists in invasive techniques.

The committee remains acutely aware of the conflict of interests inherent in providing both an adequate career structure for junior staff (especially senior registrars and university lecturers with senior registrar contracts) and a satisfactory service to patients. The problem is intensified in cardiology, with its time consuming and unpredictable emergency work as well as the high value it sets on research. Nevertheless, both the surgical and medical sides of a cardiac centre must be supported by at least one senior registrar. Junior staff, medical and surgical, will be completed by an appropriate number of registrars and senior house officers, many of whom will be undergoing general professional training on rotation schemes, which prevents exact figures being specified. As at present, attachment of trainees from overseas should be encouraged. In addition to these, further consultant and junior staff will be needed in centres which also undertake a significant quantity of paediatric, and in particular infant, cardiology (see below).

The committee does not, on this occasion, outline the demands made by such a centre on other specialties, such as anaesthetics, radiology, or pathology, or on nursing and technical services, believing that these can only be decided by local circumstances based upon the framework of cardiological and surgical staffing given above. It reiterates, however, the fact that the burden on these services is very heavy and that staffing must be sufficient to provide 24 hour cover.

Funding for cardiology and cardiac surgery

DISTRICT AND REGIONAL FUNDING

The running costs of cardiology and cardiac surgery are met through the district health authorities in which the units are situated, except in the case of the London postgraduate teaching hospitals, which are managed by special authorities and funded directly by the DHSS. Though detailed policies for revenue funding among regional health authorities vary, cardiology in district general hospitals is usually considered part of the overall district financial responsibility, whereas a cardiac centre which undertakes invasive investigation and cardiac surgery will usually be considered a regional service. Districts containing such units will receive regional funds in recognition of this role. Unfortunately, the amount a regional authority allocates for this purpose is often concealed, leading to unnecessary and wasteful controversy. Regional services must not be placed in competition with district specialties at a local level. Allocations to districts must be identified, and protected, thus enabling all parties to act responsibly. Where a district general hospital undertakes work normally done in a regional cardiac centre (for example, permanent cardiac pacing), this should attract regional funds. Similarly, regional funding should be available for expensive capital equipment wherever it is sited. Competition with the funding of district services is unacceptable.

SUPRAREGIONAL FUNDING

Infant cardiac surgery, and its associated cardiological service (see below), and cardiac transplantation are carried out in only a few centres in the country and as such should be funded supraregionally.

Research

In the rapidly expanding field of cardiology, advances can only be made against a background of research activity. Some research will be purely clinical, involving for instance the documentation of surgical results, the natural history of disease, or haemodynamic studies. For these, computer facilities for data storage and retrieval are necessary. Much research, however, will be basic experimental work which is of vital importance, and facilities for laboratory and animal work will be needed. Each unit should undertake a programme of research, the nature of which will depend on local circumstances. Contracts for consultant staff should, where appropriate, include research sessions.

Monitoring of results of cardiac investigation and surgical operations

In its previous report, the committee recomended annual reviews of the results of cardiac investigation and surgical operations. In recent years, valuable information has been collected by, for example, the Society of Thoracic and Cardiovascular Surgeons, which now has complete data on all cardiac surgical operations in the United Kingdom and Northern Ireland since 1977,[2] and the British Pacing Group. The reviews of cardiac facilities and staffing by the British Cardiac Society and the Royal College of Physicians[3] have been of great importance. The Committee considers that the organisation of similar surveys should be undertaken in other areas, particularly those related to the introduction of new and potentially hazardous techniques. Angioplasty and intracoronary thrombolysis would be good examples. The DHSS should be requested to give active support, as it has to the British Pacing Group, in the creation of such registers.

Paediatric cardiology and cardiac surgery

In children, cardiological and cardiac surgical needs are best separated into those of infants (under 1 year), many of whom are seriously ill or emergencies, and those of older children. The special requirements of the former were recognised in the Second Report, which urged the establishment of supraregional centres to deal with the predictable demands in this field. The recommendation has received support elsewhere,[4] and a working party of the Joint Consultants Committee recently formalised this proposal by naming suitable centres for England and Wales.

The DHSS has recently endorsed the establishment of nine such centres to be funded supraregionally (Birmingham, Bristol, the Brompton, Great Ormond Street, Guy's, Leeds, Liverpool, Newcastle, and Southampton). The committee welcomes this development but stresses that as nine centres are an absolute maximum, given the calculations made in the Second Report, no consideration should be given to the establishment of further such centres unless there is a considerable increase in workload which, at present, seems highly unlikely.

Such supraregional centres will, of course, also undertake the care of older children with heart disease, but the committee considers it important that these patients should continue, as at present, to be cared for at all cardiac centres, not just at those which house a supraregional service.

General paediatricians have a vital role, being the first to evaluate virtually all infants and children with heart disease. Paediatric cardiologists, therefore, must maintain the closest liaison with them, both clinically and in an educational capacity. Senior registrars in paediatrics should be given experience of infant cardiology in a supraregional centre and of general paediatric cardiology either there or in a regional cardiac centre. Particular attention should be paid to the dissemination of expertise in cross sectional echocardiography, both to paediatricians in training and those already established, since this should lead to earlier and more accurate diagnosis and referral. The physician in the district general hospital, with his expertise in echocardiography, could have a useful close liaison with the paediatricians in his hospital. In the cardiac centres, contact and collaboration with other paediatric specialties are essential.

The equipment of cardiac regional and supraregional centres must enable them to provide a service free from interruption caused by breakdowns and repairs, and here the importance of each centre having two fully equipped catheterisation laboratories can hardly by overstated. The staff of a supraregional centre must include a minimum of two surgeons to maintain 24 hour, year round cover. In some centres they may also undertake adult work. The number of paediatric cardiologists may vary from two to four, depending on the unit's size; all would normally have general paediatric expertise. Senior registrars in cardiology and cardiac surgery should rotate through these centres, and there will be a number of posts for those wishing to specialise in paediatric work. When a supraregional centre is part of a regional cardiac centre, these staff will be extra to those required for adult work, but in the other cardiac centres the care of older children will be undertaken by members of staff with paediatric training who may, for reasons of numbers, also combine this with adult cardiology.

Future review

As with the Second Report, the committee anticipates that revision of the third will be necessary within the next five years because of developments in cardiology and cardiac surgery.

Members of the Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England: R W Emanuel (chairman), N Conway (honorary secretary), R Balcon, D A Chamberlain, P B Deverall, T A H English, D G Julian, F J Macartney, D J Parker, G M Rees, Sir Keith Ross, C E Sissons, G H Smith, P J D Snow.

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Haemostatic factors and ischaemic heart disease

The Caerphilly study

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SUMMARY In a preliminary report from the Caerphilly study four haemostatic factors showed univariate associations with prevalent ischaemic heart disease after adjusting for age. These factors were fibrinogen concentration, plasma viscosity, white cell count, and the heparin-thrombin clotting time. Age and these haemostatic variables were entered into a stepwise multiple logistic regression analysis; after age the white cell count and heparin-thrombin clotting time remained significantly associated with ischaemic heart disease. Further regression analyses indicated that diastolic blood pressure contributed additionally to this association with ischaemic heart disease but that smoking habit did not.

Epidemiological studies have indicated that existing risk factors such as plasma cholesterol concentration, smoking habit, and hypertension predict only a modest proportion of new cases of ischaemic heart disease.[1] Data on possible haemostatic mechanisms in the pathogenesis of ischaemic heart disease are scarce, but two prospective studies have indicated that haemostatic factors may be independently predictive of ischaemic heart disease and stroke respectively.[2 3] A recent postmortem case series of subjects with ischaemic heart disease who had died within six hours after the onset of chest pain found coronary thrombi present in 74% of cases.[4] No intraluminal thrombi were found in age matched controls.

These reports provide evidence that haemostatic factors may be implicated in the pathogenesis of ischaemic heart disease. Several such factors are being investigated in the Caerphilly prospective study. Preliminary data are available for cases of ischaemic heart disease defined cross sectionally by the use of a standardised questionnaire[5] and a 12 lead electrocardiogram. These data form the basis of the present report.

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Subjects and methods

STUDY POPULATION

A random sample of men was drawn from the electoral registers for the town of Caerphilly, Mid Glamorgan, and two outlying villages (population 38 000). All men were sent an initial letter but were considered to be eligible only if born between, or in, 1911 and 1949—that is, were aged between 30 and 69 at the time of the survey. A total of 797 men came into this category and were invited to attend a local clinic. They were seen from September 1979 to September 1980.

SURVEY METHODS

Detailed medical questionnaires, which included the London School of Hygiene questionnaire on ischaemic heart disease,[5] were administered at an evening clinic; anthropometry[6] and 12 lead electrocardiography were carried out. Casual blood pressures were measured by a single observer using a Hawksley random zero sphygmomanometer.[7] Electrocardiographic tracings were coded independently by two experienced observers according to the Minnesota convention.[5] Subjects were classified as having ischaemic heart disease if any of the following criteria were satisfied: a definite history of myocardial infarction (chest pain defined by the London School of Hygiene questionnaire with hospital admission in excess of five days plus doctor's diagnosis); angina

Table 1 *Number (%) of men with or without ischaemic heart disease (IHD), according to age*

	Age (years)			*Total*
	30–44	*45–54*	*55–69*	
No IHD	297 (90)	141 (78)	143 (71)	581 (82)
Any IHD	33 (10)	39 (22)	58 (29)	130 (18)

(defined by the same questionnaire); Q, ST, or T wave changes or left bundle branch block (Minnesota codes 1.1–1.3, 4.1–4.4, 5.1–5.3, or 7.1) on the electrocardiogram.

Each man was invited to attend an early morning clinic, where a single venous blood sample was taken with minimum stasis after a minimum fast of eight (mean 12) hours. Aliquots were placed in two tubes containing sodium citrate (3·8%) and one containing edetic acid. Plasma was separated, usually within one hour after collection.

LABORATORY METHODS

Fibrinogen concentration was estimated by two methods; a nephelometric determination after heat precipitation in buffered saline (Fibrinogen N)[8] and a clotting assay (Fibrinogen C).[9] Plasma viscosity was estimated on plasma in edetic acid by the method of Harkness.[10] The heparin neutralising activity of platelet poor plasma was measured using the heparin-thrombin clotting time.[11] A test of dilute thrombin clotting time[11] was also carried out and was used in part to screen out samples that may have been affected by partial clotting. A value of ≥25 s for the dilute thrombin clotting time was used. Subjects with values above or equal to this had a mean heparin-thrombin clotting time of 82 s, whereas subjects with a thrombin time of <25 s had a mean heparin-thrombin clotting time of 31 s. Samples from six subjects, two of whom had some evidence of ischaemic heart disease and four of whom did not, were excluded on these grounds. Antithrombin III concentrations were estimated using a chromogenic assay (antithrombin III C)[12] and also immunologically (antithrombin III I).[13]

A full blood count, which included a white cell and platelet count, was done using a Coulter model S-plus cell counter in whole blood anticoagulated with edetic acid. Cell counts were carried out within four to 10 (mean six) hours after venepuncture and the nephelometric fibrinogen and plasma viscosity usually within 12 hours after collection. The assays on platelet poor plasma (the heparin-thrombin clotting time, thrombin time, and clottable fibrinogen) were carried out after a standard delay overnight of 28 to 32 hours. In hot or warm weather conditions a frozen cooler pack was placed inside the container. Antithrombin III assays were carried out in large batches on platelet poor citrated plasma frozen at −20°C and stored for up to three months.

A 5% sample of duplicate samples was presented "blind" to each laboratory during the course of the study. The coefficients of variation of the duplicate pairs for fibrinogen N and fibrinogen C concentrations, viscosity, white cell count, heparin-thrombin clotting time, platelet count, and antithrombin III C and antithrombin III I concentrations were 7%, 11%, 2%, 3%, 24%, 7%, 11%, and 10%, respectively. A second blood sample was taken from a small group of men (n=8–12) some four to 12 weeks after the initial sample. Coefficients of variation for these pairs of results for fibrinogen N and fibrinogen C concentrations, viscosity, white cell count, and heparin-

Table 2 *Mean (SD) values of haemostatic variables in subjects with or without any evidence of ischaemic heart disease (IHD)*

Variable	*Age (years)*	*No IHD*		*Any IHD*	
		No of subjects	*Mean (SD)*	*No of subjects*	*Mean (SD)*
Fibrinogen N (g/l)	<45	286	3·2 (0·7)	33	3·6 (0·8)
	45–54	134	3·6 (0·8)	37	3·9 (0·8)
	55–69	141	3·8 (1·0)	57	4·1 (0·8)
Fibrinogen C (100/s)	<45	279	7·1 (1·4)	29	7·7 (1·5)
	45–54	130	7·5 (1·5)	33	7·8 (1·8)
	55–69	138	8·0 (1·5)	56	8·5 (1·7)
Viscosity (cP)	<45	286	1·68 (0·09)	33	1·70 (0·10)
	45–54	132	1·71 (0·09)	38	1·76 (0·14)
	55–69	142	1·74 (0·13)	57	1·75 (0·13)
Heparin-thrombin clotting time* (log s)	<45	275	29·7 (14–62)	29	25·6 (12–55)
	45–54	128	30·0 (14–64)	33	27·2 (11–69)
	55–69	138	28·9 (14–61)	55	24·7 (12–49)
White cell count* (log 10^9/l)	<45	287	7·0 (4·1–12·0)	33	7·6 (4·2–13·8)
	45–54	135	7·1 (4·1–12·1)	38	7·5 (4·2–13·6)
	55–69	142	7·0 (4·4–11·3)	57	8·1 (4·6–14·3)

Fibrinogen N, nephelometric; fibrinogen C, clottable.
*For log transformed variables the mean is the antilog of the mean value on the log scale. Range values given are the antilogs of mean −2SD and mean +2SD on the log scale—that is, the range within which 95% of the values lie.

Table 3 *Correlation matrix for haemostatic variables and age*

	Fibrinogen N	*Fibrinogen C**	*Viscosity*	*Heparin-thrombin clotting time†*	*White cell count†*
Age	0·34	0·30	0·24	−0·08	−0·06
Fibrinogen N		0·62	0·60	−0·43	0·41
Fibrinogen C*			0·47	−0·66	0·31
Viscosity				−0·33	0·25
Heparin-thrombin clotting time†					−0·34

Fibrinogen: N, nephelometric; C, clottable.
*Measured as 100/s.
†Transformed to logarithms.
Numbers of pairs of values on which correlation coefficients are based range from 646 to 692. All coefficients are significantly different from zero at p < 0·001 except those between heparin-thrombin clotting time and age when p < 0·05 and between white cell count and age, which is not significant.

thrombin clotting time were 10%, 18%, 2%, 11%, and 21% respectively.

Results

Of 797 men eligible for inclusion in the study, 711 (89%) were examined and 700 (88%) provided a blood sample. Where tables include fewer than 700 observations a test may not have been carried out owing to insufficient blood or some other technical reason.

Subjects were classified as having ischaemic heart disease if one or more of the criteria described above were satisfied. Table 1 shows that 33 subjects (10%) aged 30 to 44 and 58 (29%) aged 55–69 had some evidence of ischaemic heart disease classified by the use of epidemiological criteria.

The relation between ischaemic heart disease and the haemostatic variables was examined in a series of detailed analyses. Several of the haemostatic variables were dependent on age, and after age adjustment five of the haemostatic variables showed significant associations with ischaemic heart disease: fibrinogen N concentration (p<0·001), fibrinogen C concentration (p<0·01), viscosity (p<0·05), white cell count (p<0·001), and heparin-thrombin clotting time (p<0·001). Two variables (heparin-thrombin clotting time and white cell count) had distributions that were appreciably skewed, and in all analyses these data were transformed to logarithms. Platelet count and the two assays for antithrombin III did not show significant associations with ischaemic heart disease, and most subsequent analyses do not include these variables.

Table 2 shows the mean values of the five haemostatic variables that were significantly associated with ischaemic heart disease by age and ischaemic heart disease category.

Table 3 shows the correlation matrix for the five haemostatic variables and age. There were highly significant (p<0·001) associations between the haemostatic variables; those between the fibrinogen concentrations and viscosity and between the fibrinogen concentrations and heparin-thrombin clotting time were particularly strong. The associations between age and the haemostatic variables were much less pronounced. There were significant positive associations between fibrinogen concentrations, viscosity, and age. The correlation coefficients between heparin-thrombin clotting time and age and between white cell count and age were both very small.

Age and the five haemostatic variables were then entered into a stepwise multiple logistic regression analysis with prevalent ischaemic heart disease as the dependent variable. Table 4 shows a summary of the results. Age entered the regression model first followed by white cell count and heparin-thrombin clotting time. Neither the fibrinogens nor viscosity added significantly to this basic model. Regression coefficients were standardised by transforming each independent variable to zero mean and unit standard deviation. The regression coefficients for the different variables are thus directly comparable.

Smoking habit was strongly related to many of the haemostatic variables. Table 5 shows that cigarette smokers had a much higher mean white cell count and much lower mean heparin-thrombin clotting time than non-smokers, while exsmokers and cigar and pipe smokers held an intermediate position.

The addition of smoking habit to the basic regression model did not add significantly to the model and did not affect the coefficients for white cell count and heparin-thrombin clotting time in other than a trivial

Table 4 *Standardised regression coefficients (SE) from stepwise multiple logistic regression*

Variable	*Standardised coefficient† (SE)*		*t*
Age	0·596	(0·112)	5·3***
White cell count‡	0·387	(0·116)	3·3***
Heparin-thrombin clotting time‡	−0·239	(0·118)	−2·0*

p < *0·005;***0·001.
†Regression coefficient standardised by transforming independent variable to zero mean and unit standard deviation.
‡Transformed to logarithms.

Table 5 *Effect of smoking habit on white cell count and heparin-thrombin clotting time*

Smoking habit	*White cell count*		*Heparin-thrombin clotting time*	
	No of subjects	*Mean (95% CI)**	*No of subjects*	*Mean (95% CI)**
Non-smoker	129	6·0 (5·8–6·2)	120	33·9 (31·8–36·1)
Ex-smoker	173	6·4 (6·2–6·6)	164	31·1 (29·2–33·2)
Cigar/pipe smoker	74	7·2 (6·8–7·7)	73	29·4 (26·9–32·1)
Cigarette smokers:				
1–14/day	92	8·1 (7·7–8·5)	87	25·9 (24·1–27·9)
15–24/day	113	8·4 (8·0–8·8)	112	25·7 (24·1–27·4)
≥25/day	107	8·2 (7·8–8·6)	98	25·7 (24·1–27·5)

*Mean values and 95% confidence interval (CI) for the mean were calculated on logarithmic scale and transformed back to natural units.

manner. For the purpose of this analysis smoking habit was treated as a factor at six levels (Table 5). A similar lack of effect was found when alcohol consumption and obesity (Quetelet's index) were added to the basic model. The addition of diastolic blood pressure significantly improved (χ^2 = 8·6; p<0·01) the fit of the model but did not alter the association between prevalent ischaemic heart disease and either white cell count or heparin-thrombin clotting time. Table 6 shows the values of the standardised regression coefficients obtained. The addition of systolic instead of diastolic blood pressure yielded a similar but slightly weaker effect (χ^2 = 6·6; 1 df; p<0·01). Values of χ^2 for the non-significantly associated variables were as follows: smoking habit (2·0, 5 df); nephelometric fibrinogen concentration (1·4, 1 df); amount of clottable fibrinogen (0·1, 1 df); log alcohol (0·7, 1 df); Quetelet's index (0·1, 1 df); viscosity (0·1, 1 df).

Discussion

This report indicates that certain haemostatic factors have a close association with prevalent ischaemic heart disease. This largely confirms the findings of a pilot study among the population of Speedwell in Bristol, in which identical laboratory techniques were used in the case of fibrinogen, heparin-thrombin clotting time, and viscosity.[14] It is fully compatible with the concept of a hypercoagulable state, shown to be associated with incident ischaemic heart disease in an early report.[2] Many haemostatic factors are rapidly modified by stressful stimuli or as a response to infection in the "acute phase response"[15 16]; among these factors are fibrinogen and white cell count, which both show strong univariate (but age adjusted) associations with prevalent ischaemic heart disease in the present data. Smoking habit is also associated with higher than average concentrations of fibrinogen[17 18] and white cell count; and also with increased heparin neutralising activity of plasma reflected in the decrease of heparin-thrombin clotting time. The present data, however, fail to show an association between prevalent ischaemic heart disease and smoking habit. This is true of both largely symptomatic subjects and asymptomatic subjects. This is contrary to expectations generated by prospective studies[19 20] and may be due to selection, through survival, of prevalent ischaemic heart disease compared with the complete identification in incident studies and also stopping smoking in symptomatic cases. All variables associated with the acute phase response show significant intercorrelations (Table 3) (white cell count, nephelometric fibrinogen, heparin-thrombin clotting time, and viscosity). Further regression analyses, however, indicate that: any association between viscosity and ischaemic heart disease disappears when nephelometric fibrinogen concentration is included in the model; the inclusion of heparin-thrombin clotting time largely removes the association of ischaemic heart disease with amount of clottable fibrinogen (the inclusion of nephelometric fibrinogen concentration removes the remainder of this association); and the addition of white cell count largely removes the contribution of nephelometric fibrinogen concentration to the basic model. As noted elsewhere, these techniques are not infallible,[21] but on the present evidence only the white cell count and heparin-thrombin clotting time show a significant association with prevalent ischaemic heart disease.

Table 6 *Standardised regression coefficients (SE) from multiple logistic regression analysis with diastolic blood pressure added to basic model*

Variable	*Standardised coefficient (SE)*		*t*
Age	0·540	(0·115)	4·7***
White cell count†	0·360	(0·117)	3·1**
Heparin-thrombin clotting time†	−0·267	(0·119)	−2·2*
Diastolic blood pressure	0·317	(0·110)	2·9**

p <*0·05; **0·01; ***0·001.
†Transformed to logarithms.

The association between white cell count and ischaemic heart disease has been reported previously for incident ischaemic heart disease in studies in the USA,[22] France,[23] and Japan.[24] White cell count also shows an association with incident cerebrovascular disease.[25] These associations do not appear to be explained by smoking habit and encourage further prospective studies among disease free populations. A mechanism that is mediated by complement activation (C5a) and that causes clumping of granulocytes and monocytes (but not lymphocytes) and subsequent leucoembolism of small coronary vessels has been postulated.[26] Other possible mechanisms have been discussed elsewhere,[27] but larger numbers are required to test these hypotheses adequately in both prevalence and prospective studies.

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Improvement in angina pectoris with alpha adrenoceptor blockade

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SUMMARY The effects of indoramin, a selective alpha$_1$ adrenoceptor antagonist, on exercise tolerance were studied in 15 patients using a random double blind crossover protocol. All patients had chronic stable angina, for which 13 had been receiving beta adrenoceptor blocking drugs and nitrates, and these were continued unchanged throughout the study. An initial open challenge with indoramin in eight patients with chronic stable angina showed no serious adverse effects. In a dose of 25 mg three times daily indoramin prolonged exercise duration and increased oxygen consumption during exercise, while the maximal double product was unchanged. The increased exercise capacity was associated with a reduction in ST segment depression during exercise. Side effects included failure of ejaculation in one patient and tiredness in five.

These results indicate than alpha$_1$ adrenoceptor blockade may provide useful additional benefit to patients with stable angina pectoris who are already receiving beta blockers and nitrates.

Medical treatment of angina pectoris remains inadequate for many patients, despite the introduction of beta adrenoceptor blocking agents, long acting nitrates, and calcium antagonists. In addition, the side effects of these drugs—for example, bronchospasm, headache, and myocardial depression respectively—may limit their use in individual patients. The afterload and preload reducing effects of alpha adrenoceptor blockade[1] should, theoretically, be beneficial to patients with angina pectoris, but as yet there are no controlled studies available to support or refute this.

Indoramin, a selective postsynaptic alpha$_1$ adrenoceptor antagonist, reduces systemic vascular resistance[2] and preload[3 4] in man, but without the usual reflex sympathetic activation,[5 6] and is an effective antihypertensive agent.[7 8] We report the results of a double blind crossover study, in which its effects on exercise tolerance were studied in 15 patients with chronic stable angina.

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Patients and methods

STUDY POPULATION

Fifteen men (aged 42 to 67 (mean 54·6) years) were studied; Table 1 shows their clinical details. Thirteen had been receiving beta blockade and 14 long acting nitrates. All patients were limited on treadmill exercise testing by angina pectoris accompanied by horizontal or downsloping ST segment depression of $\geqslant$2 mm persisting to 80 ms beyond the J point, following the Bruce protocol.[9] These changes were observed in the anterior or anterolateral chest leads in 10 patients and in the inferior chest leads in five. Fourteen had undergone coronary arteriography which showed significant (>70% stenosis) single vessel disease in seven patients, two vessel disease in six, and three vessel disease in one. With one exception, all of these had normal left ventricular end diastolic pressures (Table 1). For ethical reasons previous antiangina treatment was continued unchanged throughout the study. All patients had had frequent attacks of exercise induced chest pain occurring in a constant and predictable pattern for at least six months before the study. There was no previous history of myocardial infarction, heart failure, or atrioventricular conduction abnormalities.

Table 1 *Clinical features of patients studied*

Case No	*Age (yr)*	*LVEDP (mm Hg)*	*No of coronary vessels affected*	*Drug treatment*
1	62	10	1	Glyceryl trinitrate
2	59	15	3	Acebutolol 400 mg/day Isosorbide dinitrate 30 mg/day
3	61	8	1	Acebutolol 400 mg/day Isosorbide dinitrate 30 mg/day Isosorbide dinitrate slow release 20 mg/day
4	59	6	1	Oxprenolol 240 mg/day Isosorbide dinitrate 60 mg/day Isosorbide dinitrate slow release 20 mg/day Aldactide 50 1 tablet twice daily
5	62	5	1	Acebutolol 200 mg/day Isosorbide dinitrate 40 mg/day
6	46	5	2	Isosorbide dinitrate 30 mg/day
7	47	7	2	Atenolol 50 mg/day Isosorbide dinitrate 30 mg/day
8	67	8	2	Metoprolol 200 mg/day Dyazide two tabs/day
9	56	4	2	Nadolol 320 mg/day Isosorbide dinitrate 30 mg/day
10	43	7	1	Propranolol 160 mg/day Isosorbide dinitrate 40 mg/day
11	48	8	1	Acebutolol 400 mg/day Isosorbide dinitrate 80 mg/day
12	55	7	2	Propranolol 40 mg/day Isosorbide dinitrate 60 mg/day
13	58	—	Not known	Propranolol 160 mg/day Isosorbide dinitrate 40 mg/day
14	54	7	2	Propranolol 160 mg/day Isosorbide dinitrate 40 mg/day
15	42	12	1	Propranolol 160 mg/day Isosorbide dinitrate slow release 40 mg/day
Mean	54·6			

LVEDP, left ventricular end diastolic pressure.

PILOT STUDY

A pilot study was undertaken before the trial to determine the effect of indoramin, in doses of 25 mg twice daily to 50 mg twice daily, on blood pressure in patients with stable angina. This study included a further eight male patients with chronic stable angina who received indoramin 25 mg twice daily for the first week, 25 mg three times daily for the second week, and 50 mg twice daily for the third week. Blood pressure and heart rate were measured at the end of each week and a history relating to possible side effects was taken.

MAIN STUDY

The angina trial design was double blind; each patient received indoramin 25 mg three times daily and matching placebo capsules for three weeks each, separated by a washout period of one week. Twelve lead maximal exercise treadmill tests were carried out according to the Bruce protocol. Electrocardiograms were recorded before exercise, at the end of each three minute stage, at peak exercise, immediately after exercise, and at two minutes and 10 minutes after stopping exercise. Significant ST segment depression was taken as a shift of ≥2 mm 80 ms from the J point. The electrocardiograms were produced by a Picker International semiautomated electrocardiograph model CM 3400. Routine blood pressure measurements were made before, during, and after exercise.

Total body oxygen consumption was continuously measured during each exercise test using a PK Morgan oxygen analyser Model 500. This was used as a direct measure of total body work and hence an indirect measure of myocardial work during exercise.

Results were expressed as mean (standard error of mean) and comparisons were made using analysis of variance.

Results

Results of the pilot study showed that indoramin in doses of 25 mg twice daily to 50 mg twice daily had no appreciable adverse effects on these patients. Table 2

Table 2 *Effect of indoramin on blood pressure (n=8)*

Position	*Mean (SEM) pressure (mm Hg)*	
	Before indoramin	*End of week 3 (50 mg twice daily)*
	Systolic	
Lying	120 (10)	130 (4)
Standing	126 (8)	124 (6)
	Diastolic	
Lying	82 (9)	81 (6)
Standing	83 (8)	79 (4)

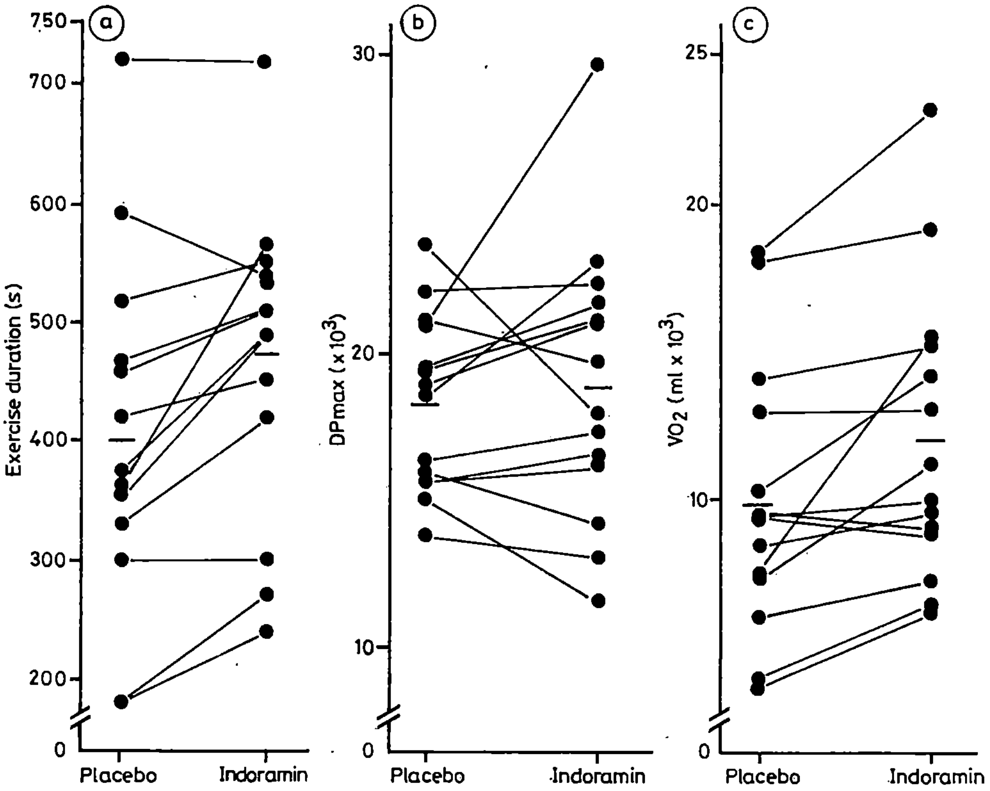

Fig. 1 *Effects of indoramin 25 mg three times daily on (a) exercise duration, (b) rate pressure product (DPmax), and (c) total oxygen consumption (VO_2) in each patient studied. The horizontal bar indicates the mean for each group.*

shows the results of blood pressure measurements. No significant changes were observed in the group as a whole, and blood pressure did not fall below 105/50 mm Hg in any patient.

EXERCISE TOLERANCE

Figure 1 shows the effects of indoramin on exercise duration and oxygen consumption during exercise. Indoramin significantly increased mean exercise duration (17%) from 402 (39) s to 470 (35) s ($p<0{\cdot}01$), and mean total oxygen consumption during exercise (21%) from 9·9 (1·2)l to 12·0 (1·3)l ($p<0{\cdot}01$). Regression analysis showed a significant correlation between oxygen consumption and exercise duration ($r=0{\cdot}75$–$0{\cdot}83$, $p<0{\cdot}01$ in each case).

Completed diary cards for all stages of the study were returned by only six patients and were considered unreliable for evaluation.

HEART RATE AND BLOOD PRESSURE DURING EXERCISE

Mean heart rate increased from 66 (3) beats/minute at

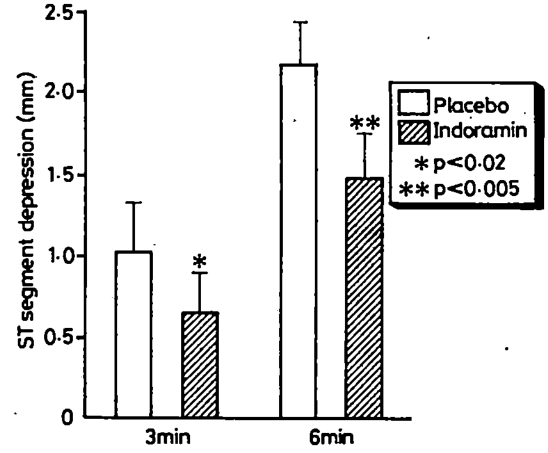

Fig. 2 *Effects of indoramin 25 mg three times daily on ST segment depression at three minutes and six minutes of exercise. Bars represent SEM.*

rest to 112 (3) beats/min at peak exercise during placebo treatment. Heart rate at peak exercise was slightly increased by indoramin (to 118 (5) beats/min from 68 (4) beats/min at rest). The rise in mean systolic pressure at peak exercise was also affected little by indoramin (161 (8) mm Hg compared with 164 (6·6) mm Hg with placebo). Thus the rate pressure product at peak exercise was not significantly affected by indoramin (18934 (1263) compared with 18311 (795) with placebo).

ST SEGMENT CHANGES

Figure 2 shows the changes in ST segment during exercise. Prolongation in exercise capacity was associated with a significant reduction in ST depression at three minutes ($p<0·02$) and six minutes ($p<0·005$) of exercise. The extent of ST depression was similar at peak exercise in each group.

SIDE EFFECTS

Failure of ejaculation occurred in one patient during active treatment, but he elected to continue the study. One patient withdrew from the study because of pronounced tiredness with active treatment. Five other patients complained of tiredness with active treatment compared with two with the placebo.

Discussion

These results indicate that alpha adrenoceptor blockade may be a useful adjunct to the treatment of stable angina pectoris in patients already receiving conventional antianginal treatment. Alpha adrenoceptor blockade has been extensively investigated in the treatment of hypertension and cardiac failure. Little is known, however, about its effect on angina pectoris. Prazosin has been shown to be unhelpful in treating variant angina.[10] Labetolol possessing both alpha and beta adrenoceptor blocking properties improves exercise tolerance in angina pectoris.[11 12] The beta blocking potency of this compound is, however, four to eight times greater than that of alpha,[13] and the contribution of alpha adrenoceptor blockade to the antianginal effect is unclear. Because of the relative paucity of information available about the effects of alpha blocking agents in patients with angina pectoris it was considered unethical to stop current treatment during this study. For this reason, the present results can be interpreted only as indicating benefit in patients already receiving beta blockers or nitrates or both.

In this study, exercise capacity before the onset of angina was improved, as indicated by increases in exercise duration and oxygen consumption during exercise. In contrast, the maximal double product changed little. These findings indicate that indoramin significantly increased total work but that cardiac work was similar at maximal exercise with placebo and active treatment. This implies that cardiac work at lower workloads was reduced by the drug, and the reduction in ST segment depression at three and six minutes of exercise supports this. This in turn suggests that the antianginal effect observed here reflects actions of the drug on peripheral arterioles and veins; however, further work is needed to clarify this. Indoramin frequently produced tiredness in the present study, and one patient withdrew for this reason. Serious cardiovascular side effects such as hypotension or worsening of angina did not occur. The incidence of side effects observed here was lower than in previous studies, in which higher doses were used to treat hypertension,[14] but is comparable with previous studies using calcium antagonists[15] and beta adrenoceptor antagonists.[16 17]

In conclusion alpha adrenoceptor blockade with indoramin produced significant improvement in exercise capacity in patients already receiving beta blockers and nitrates. Further work is needed to establish whether or not this is a general property of alpha adrenoceptor blockade and to determine its haemodynamic mode of action.

We thank the staff of the Department of Cardiology and the Lung Function Unit, Llandough Hospital, for their invaluable assistance.

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Effects of intracoronary and intravenous amrinone infusions in patients with cardiac failure and patients with near normal cardiac function

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SUMMARY The effects of intracoronary and intravenous infusions of amrinone were studied to distinguish the drug's direct cardiac actions from its peripheral vascular and neuroendocrine properties. Intracoronary infusions of amrinone were found to have no haemodynamic effect other than producing a slight reduction in the left ventricular ejection fraction and some suggestion of coronary vasodilatation in patients with impaired left ventricular function. They did not improve contractility, cardiac output, or filling pressures and had no significant effect on myocardial metabolism, although therapeutic concentrations of the drug were detected in coronary sinus blood. Intravenously administered amrinone reduced filling pressures and improved the cardiac index in all patients, but haemodynamic improvements were most pronounced in the patients with the worst cardiac function. These changes were accompanied by improvements in the indices of contractility only in patients in whom alterations in concentrations of free fatty acid, glycerol, and glucose suggested peripheral catecholamine release. In the patients with the best basal cardiac function intravenously administered amrinone produced a reduction in myocardial work and evidence of myocardial ischaemia, as a result of excessive reduction of coronary perfusion pressure and increased heart rate, without any appreciable increase in cardiac index.

It is concluded that, at the concentrations of the drug that can be achieved in man without adverse effects, amrinone has no direct positive inotropic effect. Haemodynamic changes are predominantly the result of vasodilatation, although catecholamines may be released in some patients.

Amrinone (Inocor; Winthrop-Breon, USA) is the prototype of a group of new drugs that are currently being investigated for use in the treatment of patients with heart failure. Amrinone acutely lowers cardiac filling pressures and improves cardiac output[1] without increasing myocardial oxygen consumption.[2 3] These effects have been largely attributed to the direct positive inotropic action that has been shown with the drug in normal animal myocardium.[4 5] Relatively less attention has been paid to the direct vasodilator properties of amrinone.[5 6]

In patients with cardiac failure initial small studies showed an improvement in a contractility index (maximum rate of rise of left ventricular pressure (dP/dt max)) after intravenous administration of amrinone.[7–9] These studies contained flaws in experimental design, which we have discussed previously,[10–12] not least of these being the absence of any attempt to look for a dose response relation between the amount of amrinone administered and changes in contractility. Subsequent studies that sought a dose-response relation and contained larger numbers of observations than the earlier reports found no evidence of a positive inotropic effect in patients.[3 10 13] Moreover, two of these subsequent studies compared the effects of amrinone with those of other agents commonly used in the treatment of cardiac failure. One study compared amrinone with dobutamine,[13] which possesses both positive inotropic and vasodilator properties. The authors showed no change in contractility after amrinone but an increase (partially

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heart rate related) with dobutamine; both drugs also produced changes in haemodynamics attributable to vasodilatation. In the other study amrinone was compared with a pure vasodilator, nitroprusside.[3] No difference between the effects of the two drugs was detected except for evidence that amrinone caused catecholamine release in some patients.

Because of this conflicting evidence and the difficulty of determining, by intravenous administration, the effect of drugs on the human myocardium in vivo we have investigated the effects of amrinone on the heart by administering it by intracoronary infusion.

Patients and methods

We studied eight men without significant coronary disease. Seven, aged 28–52 (mean 41) years, had dilated cardiomyopathy; of them, three gave a history of high alcohol intake. Six were in sinus rhythm and one in atrial fibrillation. All were receiving diuretics, six digoxin, and one each amiodarone, warfarin, and indomethacin. In addition, we studied a man aged 41 who gave a history of angina despite "normal coronary arteries and good left ventricular function" diagnosed at another hospital. He had been referred for investigation of the effect of atrial pacing on myocardial lactate extraction. He was receiving atenolol (100 mg daily) at the time of his investigation and had never been in cardiac failure. (Careful review of coronary angiograms after the trial showed that three patients with poor cardiac function had isolated noncritical coronary narrowings (<50%), which were thought to be insufficient in number or site to account for their global cardiac dysfunction. The patient with angina was found to have a single 80% narrowing in a very small diagonal branch.) Current drug treatment was continued until the evening before the study. The trial had the approval of the hospital ethical committee, and each patient gave his informed written consent.

Patients were studied in the morning after an overnight fast. One hour before cardiac catheterisation they were premedicated with diazepam (10 mg) and atropine (0·6 mg) intramuscularly. Heparin (45 U/kg) was given intravenously at the same time to minimise the effect of a subsequent dose of heparin on free fatty acid concentrations.[14] Right and left heart pressures were measured routinely via catheters in the right femoral vein and artery inserted under local anaesthesia with lignocaine. Immediately after arterial catheterisation a second dose of heparin (45 U/kg) was given. Coronary arteriography was performed with Urografin 370 (76%). The minimum volume of contrast (about five injections, each of 5–8 ml) was used.

A fluid filled catheter was then positioned in the pulmonary artery. A catheter tip micromanometer (No 8 French gauge Millar) was positioned in the left ventricle retrogradely across the aortic valve for measuring pressure and injecting contrast medium for left ventricular cineangiography. A selective left coronary Judkins's catheter was inserted via an additional arterial Seldinger puncture for intracoronary infusion of drugs and measurement of aortic pressure. Cardiac output was measured by dye dilution[10] and coronary sinus flow by thermodilution,[14] as previously described.

Pressures were measured with reference to the sternal angle as zero. Pressure, micromanometer, and thermistor signals were displayed on a Cambridge 12 channel recorder, stored on magnetic tape, and processed by computer. Indices of contractility, including dP/dt max, dP/dt max divided by developed pressure (dP/dt max/P),[15] the peak measured shortening velocity of the contractile element ((dP/dt/P) max),[16] and the product of the series elastic stiffness constant and the velocity of contractile shortening at zero load (KV max),[17] were derived by on line computer processing of the pressure signal.[10]

The plasma concentrations of amrinone and its metabolite, *N*-acetyl amrinone, were determined by high pressure liquid chromatography.[18] The oxygen content and concentrations of lactate, pyruvate, hydroxybutyrate, acetoacetate, glycerol, free fatty acid, and glucose in arterial and coronary sinus blood were determined as previously described.[3 14]

Myocardial oxygen consumption, left ventricular minute work, myocardial efficiency, and the myocardial extractions, extraction ratios, and oxygen extraction ratios of substrates were calculated using standard formulas.[19] Total systemic vascular resistance was taken to be mean aortic pressure divided by cardiac output. Pulmonary vascular resistance was considered to be:

$$\frac{\text{(Mean pulmonary artery pressure} - \text{diastolic pulmonary artery pressure)}}{\text{cardiac output}}$$

Coronary vascular resistance was calculated from[20]:

$$\frac{\text{(Mean aortic diastolic pressure} - \text{left ventricular diastolic pressure)} \times \text{coronary diastolic filling time}}{\text{coronary sinus flow}}$$

No measurements were made until at least 40 minutes after coronary arteriography. The patient with angina was paced to determine the effect of fast heart rates on myocardial metabolism of lactate. He was allowed to return to the basal state before undergoing the research procedure.

During the research procedure haemodynamic measurements, blood sampling, and left ventricular cineangiography were performed according to a time schedule so that observations were made at comparable intervals after test interventions. The interventions were: (1) control or basal state, (2) intracoronary lactate infusion, (3) intracoronary amrinone infusion, (4) intravenous amrinone. The order of interventions 2 and 3 was randomised. The patients were unaware of the order of the interventions. To eliminate observer bias or selection haemodynamic indices (heart rate, blood pressures, flows, and contractility indices) were calculated by computer during predetermined intervals after the start of drug administration. Biochemical analysis was performed by automatic analysis (oxygen content and glucose concentration) or by technicians unaware of the nature of the samples for analysis.

Intracoronary amrinone was administered at a rate of 0·5 mg/min. The lactate (carrier) solution used was identical in all respects to the amrinone solution except that it contained no amrinone. We have previously used this lactate solution in both in vitro[6] and in vivo[3] experiments and shown it to be without vascular or myocardial activity. The lactate solution was administered at the same rate as the amrinone solution. Six patients received intracoronary infusions of amrinone and the lactate lasting two minutes each (short infusion). Three received intracoronary amrinone first and three the lactate first. In these six patients the measurements performed two minutes after the start of the infusion were made during the infusion. Other measurements were made after the end of the infusion. In two patients (one with good left ventricular function) both intracoronary infusions were prolonged for 15 minutes (long infusion) so that all measurements were made during infusion. One of these two patients (the one with good left ventricular function) received intracoronary amrinone first. (The number of studies of long intracoronary infusion was smaller than intended because the manufacturer of amrinone withdrew all our stocks of the drug before we had completed the trial.)

In the control state heart rate, pulmonary arterial, aortic, and left ventricular pressures, contractility indices, cardiac output, and coronary sinus flow were measured, and arterial (left ventricular) and coronary sinus blood was sampled for metabolite concentrations. Single plane left ventricular cineangiography (right anterior oblique projection) was performed for calculating left ventricular volumes and the end systolic pressure volume relation. About 20 minutes was allowed for return to the basal state, which was confirmed by rechecking pressures and contractility indices. The first intracoronary infusion was started and pressures and indices of left ventricular contractility measured every two minutes for six minutes. Eight minutes after starting the intracoronary infusion all measurements including those of flows and metabolite concentrations and left ventricular cineangiography were repeated. After permitting another return to the basal state the second intracoronary infusion was started with measurements and angiography at intervals identical to those used for the first intracoronary infusion. During each intracoronary infusion coronary sinus blood was sampled for measurement of amrinone concentration. Mixed venous blood was also sampled after the long infusions in the two patients who had received these.

After a further return to the basal haemodynamic state each subject was given 1·5 mg/kg intravenous amrinone over two minutes. Measurements and angiography were performed after the start of this infusion at the same intervals as those that had been used after the start of the intracoronary infusions. Peripheral venous blood was sampled for measurement of plasma amrinone concentration after intravenous amrinone.

STATISTICAL ANALYSIS

Data on the six patients with poor left ventricular function who received short intracoronary infusions are expressed as mean (SEM). Statistical analysis for this group was by the paired t test. The initial control (basal) period was compared with the basal state before each intervention. The effects seen at all times after each intervention were compared with both the initial control period and the control period immediately before that intervention. In addition, the effects observed after intracoronary and intravenous infusion of amrinone were compared with the effects seen at the same intervals after intracoronary infusion of lactate.

The data on the two patients who received long intracoronary infusions were not amenable to statistical analysis, and the raw data are provided.

Further statistical analysis was by linear or log linear regression. Spearman's rank test was used to test for a non-parametric relation when one was sought but could not be detected using a simple algorithm. A p value of less than 0·05 was considered to be significant.

Results

PLASMA AMRINONE CONCENTRATIONS

Table 1 shows the concentrations of amrinone detected in coronary sinus blood during intracoronary infusions of amrinone in the patients studied. No *N*-acetyl amrinone was detected in the coronary sinus blood of the patients during the infusions. Table 2, which shows our total experience of the range of concentrations of amrinone found in peripheral blood

Table 1 *Plasma concentrations of amrinone in coronary sinus blood during infusion of intracoronary amrinone (0·5 mg/min)*

Case No	*Length of infusion*	*Amrinone (μg/ml)*
1	Short	0·18
2	Short	1·37
3	Short	Detectable but unquantifiable
4	Short	0·69
5	Short	1·70
6	Short	1·60
7	Long	2·07
8	Long	2·45

after infusion of 1·5 and 3·5 mg/kg intravenous amrinone and during long term oral treatment, is given for comparison. It should be noted that amrinone was detectable in venous blood after long intracoronary infusion in each of the two patients who received this, being 0·46 μg/ml in the patient with poor left ventricular function and 0·25 μg/ml in the patient with good left ventricular function.

SHORT INFUSIONS

Haemodynamics

The initial control (basal) values of all haemodynamic indices measured were the same as each set of preintervention control values.

Compared with control measurements the intracoronary infusions did not cause any alteration in heart rate, left ventricular pressures, or contractility indices either during the infusion or after the infusion had stopped (Fig. 1: only the contractility indices dP/dt max and KV max are shown; other contractility indices and dP/dt min were also unaltered). Variables measured after intracoronary infusion, including coronary sinus flow, arteriocoronary sinus oxygen difference, myocardial oxygen consumption and efficiency (Fig. 2), cardiac index, left ventricular volumes and the left ventricular end systolic pressure to volume ratio (Fig. 3), and pulmonary arterial and aortic pressures, left ventricular minute work, and systemic and pulmonary vascular resistances (Fig. 4), were also unaltered by the intracoronary infusions.

When the intracoronary infusions of amrinone and lactate were compared no significant difference was

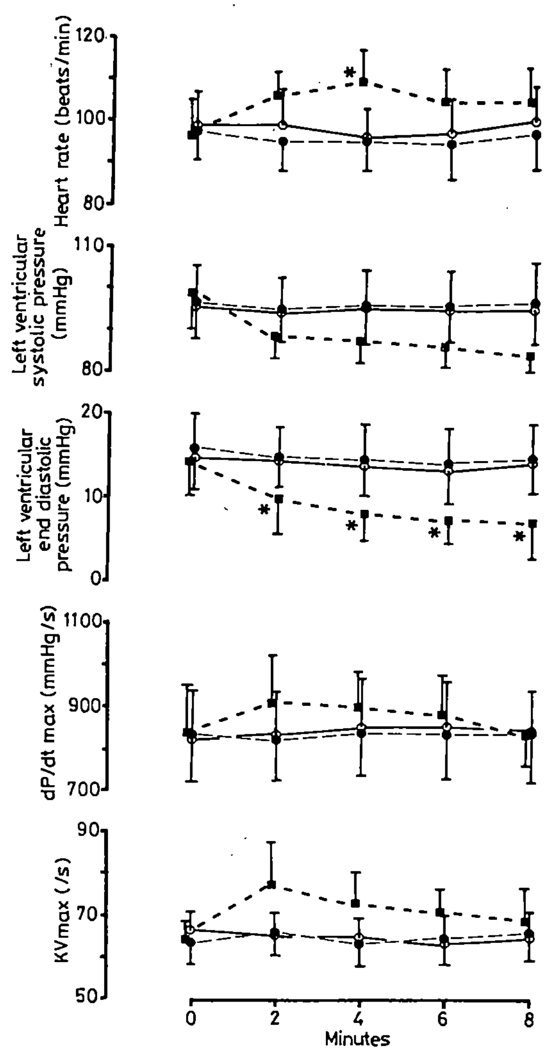

Fig. 1 *Effects of short (two minutes) intracoronary infusion of lactate (○—○) and amrinone (●---●) and of intravenous amrinone (■—■) on haemodynamics in six patients with poor left ventricular function. Infusions were administered after taking basal measurements (0 minutes) until after taking measurements at two minutes. Values shown are mean (SEM). *p<0·05.*

Table 2 *Plasma concentrations of amrinone in peripheral venous blood during acute intravenous and long term oral amrinone treatment*

Route of administration	*Dose*	*Frequency of administration*	*Interval since last dose*	*Range (mean) plasma amrinone concentrations (μg/ml)*
Intravenous	1·5 mg/kg	Once only	0–5 min 6–10 min	4–13 3–5
Intravenous	3·5 mg/kg	Once only	0–5 min 6–10 min	≤28 5–9
Oral	100 mg	Every 8 hours	2 h (peak) 8 h (trough)	0·5–6·4 (3·0) 0–5·1 (1·9)

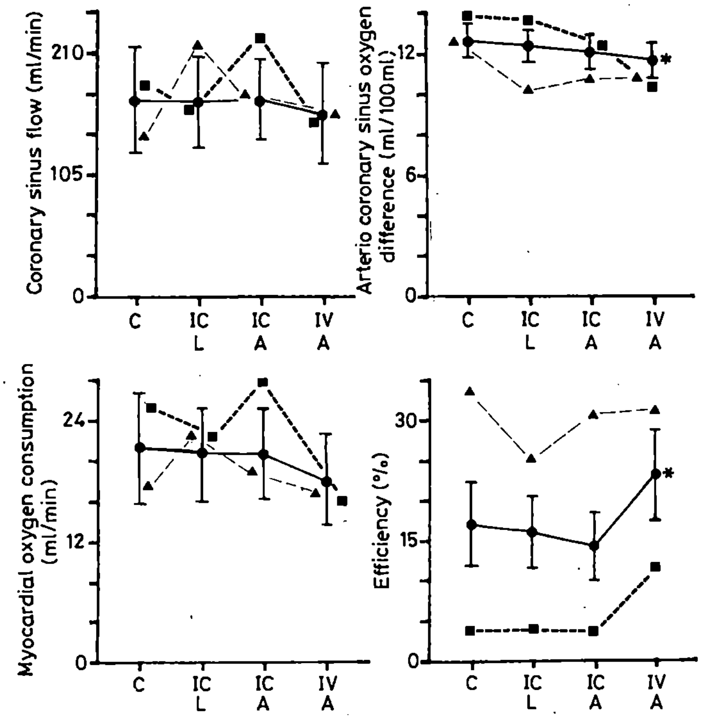

Fig. 2 *Effects of intracoronary and intravenous administration of amrinone on coronary sinus flow, arteriocoronary sinus oxygen difference, myocardial oxygen consumption, and myocardial efficiency in six patients with poor left ventricular function who received short (two minute) intracoronary infusions (mean (SEM)) (●—●) and the two patients who received long intracoronary infusions, one with good (▲—▲) and one with poor (■—■) left ventricular function. C, control; L, lactate; A, amrinone; IC, intracoronary; IV, intravenous.* *$p<0·05$.

seen for any variable measured except that left ventricular ejection fraction was slightly but significantly reduced after intracoronary infusion of amrinone. In addition, coronary vascular resistance was unaltered in one patient after the short intracoronary infusion of amrinone and reduced in the remaining five compared with intracoronary lactate, but the mean value failed to achieve significance (Fig. 5).

In contrast, in these six patients intravenous amrinone produced a significant ($p<0·05$) increase in heart rate at four minutes and a significant ($p<0·05$) reduction in left ventricular end diastolic pressure at all times after the intervention (Fig. 1). The reduction in left ventricular systolic pressure after intravenous amrinone just failed to achieve significance at all times shown ($0·05<p<0·1$). Slight increases in indices of contractility were seen but did not achieve significance when compared with control data and measurements made at the same intervals after the intracoronary infusion of lactate. Intravenously infused amrinone also produced significant reductions in arteriocoronary sinus oxygen difference, left ventricular end diastolic volume index, pulmonary arterial and aortic pressures, and systemic vascular resistance and produced increases in cardiac index, left ventricular ejection fraction, left ventricular minute work, and efficiency (Figs. 2, 3, and 4). Coronary sinus flow, myocardial oxygen consumption, pulmonary and coronary vascular resistances, and the left ventricular end systolic pressure to volume ratio were not significantly altered.

Metabolism

The short intracoronary infusion of lactate produced a significant increase in arterial pyruvate concentration, myocardial pyruvate extraction, and myocardial pyruvate extraction ratio compared with control values. Intracoronary amrinone produced a significant increase in myocardial pyruvate extraction, but the increases in arterial pyruvate concentration and

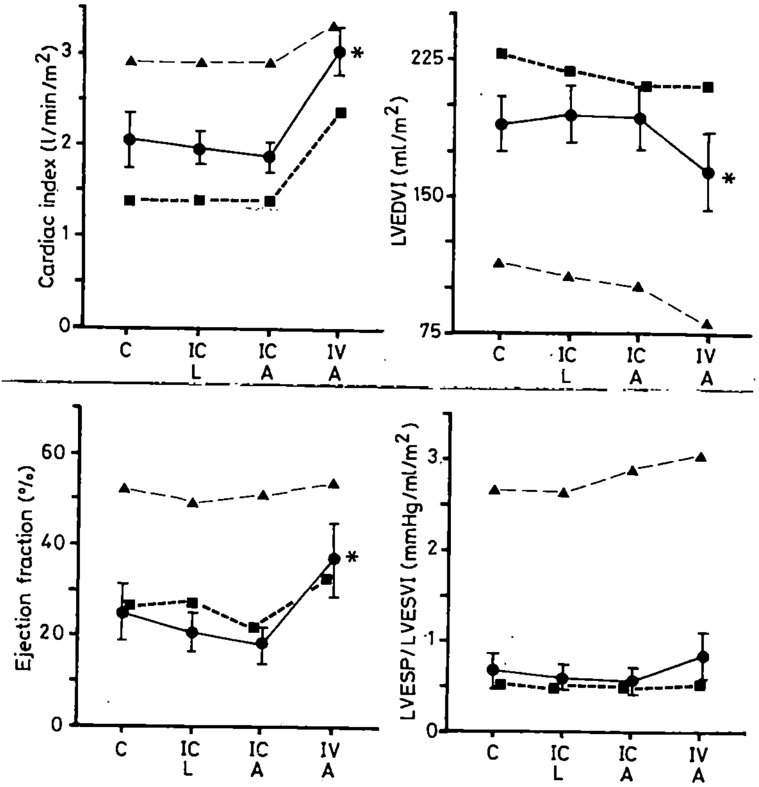

Fig. 3 *Effects of intracoronary and intravenous infusion of amrinone on cardiac index, left ventricular end diastolic volume index (LVEDVI), left ventricular ejection fraction, and left ventricular end systolic pressure/volume index (LVESP/LVESVI) in six patients with poor left ventricular function who received short (two minute) intracoronary infusions (mean (SEM)) (●—●) and two patients who received long intracoronary infusions, one with poor (■---■) and one with good (▲—▲) left ventricular function. C, control; L, lactate; A, amrinone; IC, intracoronary; IV, intravenous.* $^*p<0{\cdot}05$.

myocardial pyruvate extraction ratios were not significant compared with control values. The effects of intracoronary lactate and intracoronary amrinone on pyruvate metabolism were not significantly different. Intravenous amrinone had no significant effect on pyruvate metabolism (Table 3).

Short intracoronary infusions of both amrinone and lactate and the administration of intravenous amrinone in these six patients had no significant effect on arterial or coronary sinus concentrations, myocardial extractions, or extraction ratios of lactate, glycerol, free fatty acid (Table 3), or ketone bodies (not tabulated). The mean arterial plasma concentrations of glycerol and free fatty acid rose after intravenous administration of amrinone because considerable increases (>40%) developed in two patients.

Samples of plasma for estimation of glucose concentration were unfortunately destroyed in two of the six patients who received the short intracoronary infusions. In the remaining four patients intracoronary infusions produced no detectable effect on the arterial or coronary sinus concentrations of glucose. A small effect could have been masked by the general tendency for the arterial glucose concentration to decline with time (presumably the result of fasting). In each patient, however, intravenous amrinone produced a rise in arterial and coronary sinus glucose concentration compared with the preceding estimation. The mean increase for both arterial and coronary sinus concentrations was 1·2 mmol/l.

LONG INFUSIONS

Haemodynamics

The patient with dilated cardiomyopathy who

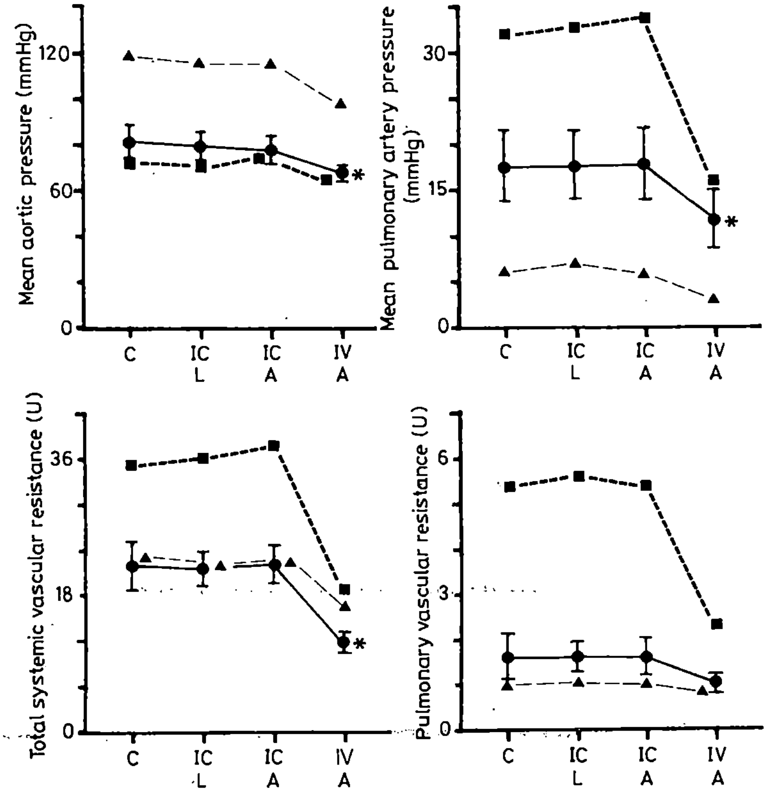

Fig. 4 *Effects of intracoronary and intravenous infusion of amrinone on mean aortic pressure, mean pulmonary artery pressure, total systemic vascular resistance, and pulmonary vascular resistance in six patients with poor left ventricular function who received short (two minute) intracoronary infusions (mean (SEM)) (●—●) and two patients who received long intracoronary infusions, one with poor (■---■) and one with good (▲---▲) left ventricular function. C, control; L, lactate; A, amrinone; IC, intracoronary; IV, intravenous.* $*p<0{\cdot}05$.

received the long intracoronary infusions had preintervention haemodynamic indices comparable to or slightly worse than those for the six patients who received the short intracoronary infusions. The other patient who received long intracoronary infusions had good left ventricular function as judged from heart rate, filling pressures, cardiac index, left ventricular ejection fraction, and indices of contractility.

In both patients when compared with values in the control state and during intracoronary infusion of lactate the long intracoronary infusion of amrinone did not cause any consistent alteration in left ventricular pressures or indices of contractility (Figs. 6 and 7), cardiac index or variables derived from left ventricular angiography (Fig. 3), pulmonary arterial and aortic pressures, left ventricular minute work, or systemic or pulmonary vascular resistances (Fig. 4). In the patient with poor left ventricular function coronary sinus flow increased and coronary vascular resistance fell after intracoronary infusion of amrinone, but opposite changes were seen in the patient with good left ventricular function (Figs. 2 and 5).

After receiving intravenous amrinone the patient with poor left ventricular function showed a transient rise in heart rate (maximum four minutes after the start of the infusion) and a later reduction in left ventricular filling pressure (Fig. 6). Contractility indices were increased in this patient after the intravenous dose of amrinone, although no improvement in contractility had been seen during the intracoronary amrinone infusion. Changes in other haemodynamic indices—for example, heart rate, blood pressures, and flows—after intravenous amrinone in this patient, however, were comparable with those observed after

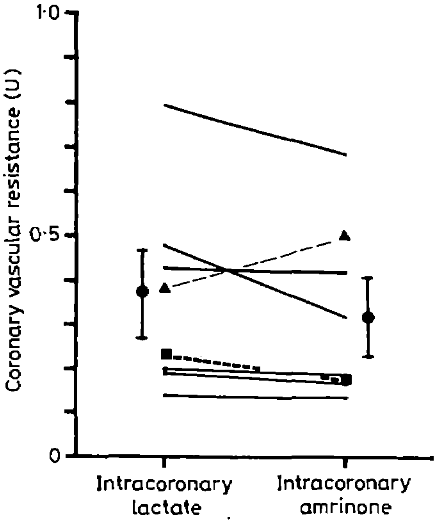

Fig. 5 *Effect of intracoronary amrinone on coronary vascular resistance in six patients who received short (two minute) intracoronary infusions (———) (mean (SEM) for all six represented by ●) and two patients who received long intracoronary infusions, one with poor left ventricular function (■---■) and one with good left ventricular function (▲---▲).*

intravenous amrinone in the six patients who received short intracoronary infusions (Figs. 2, 3, and 4).

The responses seen after intravenous amrinone in the seven patients with poor left ventricular function differed a little from those observed in the patient with good left ventricular function. In this patient a reduction in left ventricular pressures also occurred, but the decrease in left ventricular systolic pressure was considerable (Fig. 7). This was accompanied by a large increase in heart rate and contractility indices (Fig. 7). The slight increase in cardiac index seen was due to the increase in heart rate, as left ventricular end diastolic volume and ejection fraction were unaltered (Fig. 3). Pulmonary arterial and aortic pressures and systemic vascular resistance were considerably reduced after intravenous amrinone (Fig. 4). In contrast to the changes in arteriocoronary sinus oxygen difference, left ventricular minute work, and efficiency observed after intravenous amrinone in the patients with poor left ventricular function, a slight reduction in minute work and no real alteration in efficiency or arteriocoronary sinus oxygen difference developed in the patient with good left ventricular function (Fig. 2).

Metabolism

The metabolic effects of the long intracoronary infusions of amrinone and the lactate solution are difficult to determine as during the periods of sampling for metabolites both the subjects were receiving an

Table 3 *Metabolic effects of interventions in patients who received short intracoronary infusions. Figures are mean (SEM) values*

	Arterial concentration (mmol/l)	*Coronary sinus concentration (mmol/l)*	*Extraction (mmol/l)*	*Extraction ratio (%)*
		Lactate		
Control	0·488 (0·083)	0·373 (0·073)	0·115 (0·040)	23·2 (7·8)
Intracoronary lactate	0·514 (0·054)	0·326 (0·049)	0·187 (0·068)	34·0 (9·5)
Intracoronary amrinone	0·489 (0·065)	0·295 (0·046)	0·194 (0·060)	37·8 (8·1)
Intravenous amrinone	0·515 (0·054)	0·361 (0·068)	0·154 (0·083)	27·2 (13·0)
		Pyruvate		
Control	0·046 (0·010)	0·041 (0·004)	0·004 (0·011)	−9·3 (20·0)
Intracoronary lactate	0·057 (0·010)*	0·036 (0·004)	0·021 (0·011)*	25·8 (16·0)*
Intracoronary amrinone	0·048 (0·008)	0·035 (0·005)	0·013 (0·012)*	14·5 (18·2)
Intravenous amrinone	0·054 (0·011)	0·049 (0·005)	0·006 (0·013)	−11·4 (25·9)
		Glycerol		
Control	0·088 (0·017)	0·075 (0·015)	0·013 (0·007)	7·1 (14·2)
Intracoronary lactate	0·079 (0·020)	0·071 (0·023)	0·008 (0·006)	18·7 (10·2)
Intracoronary amrinone	0·081 (0·024)	0·067 (0·022)	0·014 (0·012)	12·1 (16·1)
Intravenous amrinone	0·140 (0·051)	0·108 (0·030)	0·032 (0·029)	15·7 (8·0)
		Free fatty acid		
Control	0·66 (0·09)	0·63 (0·09)	0·03 (0·05)	4·5 (7·3)
Intracoronary lactate	0·54 (0·12)	0·67 (0·10)	−0·13 (0·10)	−35·5 (22·3)
Intracoronary amrinone	0·59 (0·13)	0·67 (0·14)	−0·08 (0·08)	−21·6 (23·3)
Intravenous amrinone	0·81 (0·18)	0·75 (0·12)	0·06 (0·11)	−2·6 (10·1)
		Glucose (n=4)		
Control	7·93 (1·21)	5·55 (0·29)	2·38 (1·03)	26·3 (8·7)
Intracoronary lactate	6·35 (0·54)	6·25 (0·62)	0·10 (0·76)	−0·1 (12·4)
Intracoronary amrinone	6·60 (0·28)	5·63 (0·30)	0·98 (0·30)	14·6 (2·2)
Intravenous amrinone	7·40 (0·82)	6·78 (0·45)	0·63 (0·62)	6·3 (7·6)

*Significance compared with control $p<0·05$.

Conversion: SI to traditional units—Lactate: 1 mmol ≈ 90 mg. Pyruvate: 1 mmol ≈ 88 mg. Glycerol: 1 mmol ≈ 217 mg. Glucose: 1 mmol ≈ 180 mg.

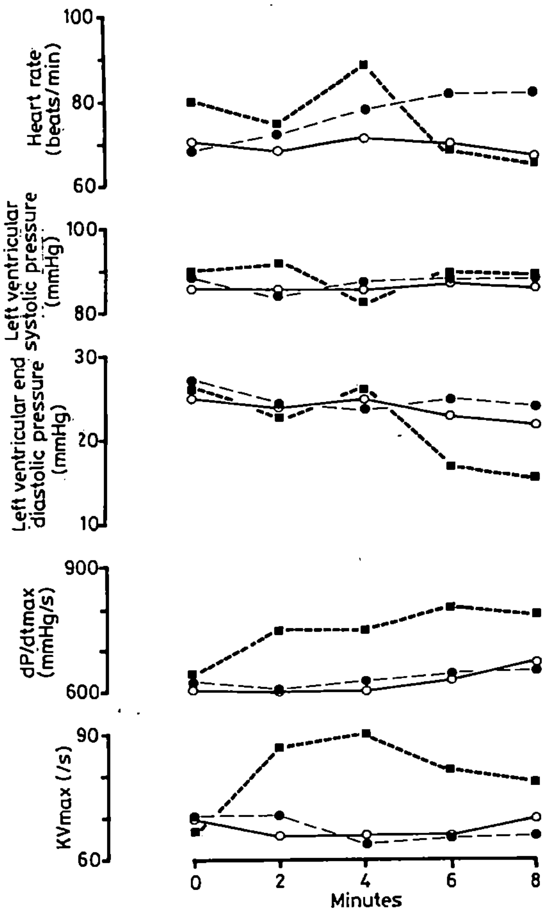

Fig. 6 *Effect of long intracoronary infusion of lactate* (○—○) *and amrinone* (●---●) *and intravenous infusion of amrinone* (■---■) *on haemodynamics in the patient with poor left ventricular function. Infusions were administered after taking basal measurements (0 minutes).*

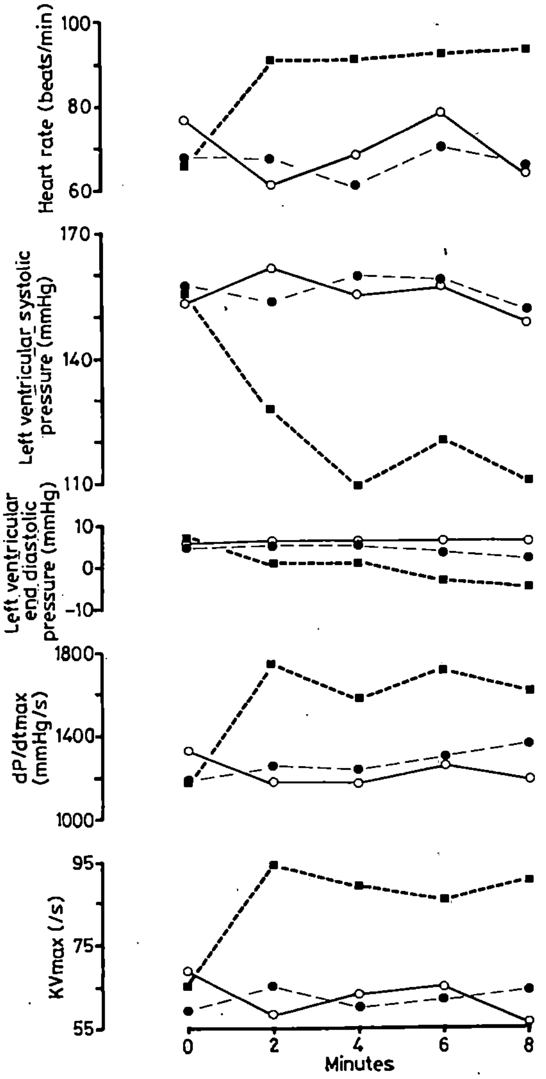

Fig. 7 *Effect of long intracoronary infusion of lactate* (○—○) *and amrinone* (●---●) *and intravenous infusion of amrinone* (■---■) *on haemodynamics in the patient with good left ventricular function. Infusions were administered after taking basal measurements (0 minutes).*

intracoronary lactate load from the infusion itself. It was thus difficult to know precisely the lactate concentration of blood flowing down the left coronary artery. This would be dependent on the lactate concentrations in arterial blood and the infusion solutions and the relative contribution of each of these to the blood in the left coronary artery. These factors would also influence, to a lesser extent, the concentrations of other metabolites in the left coronary artery. (As the volume of infusate per minute was small compared with coronary sinus flow rate it should introduce only a small or negligible volume effect to changes in myocardial oxygen consumption occurring as a result of pharmacological properties of the infusate.) The analysis of coronary sinus blood during these long infusions showed high concentrations of all myocardial metabolites measured, particularly lactate (Table 4); but the amrinone and lactate infusions had similar effects.

After the subsequent intravenous dose of amrinone, arterial lactate concentrations were altered little, although the myocardial lactate extraction ratio became negative in the patient with good left ventricu-

Table 4 *Metabolic effects of interventions in patients who received long term intracoronary infusions*

	Patient with poor left ventricular function				*Patient with good left ventricular function*			
	Arterial concentration (mmol/l)	*Coronary sinus concentration (mmol/l)*	*Extraction (mmol/l)*	*Extraction ratio (%)*	*Arterial concentration (mmol/l)*	*Coronary sinus concentration (mmol/l)*	*Extraction (mmol/l)*	*Extraction ratio (%)*
			Lactate					
Control	0·560	0·366	0·194	34·6	0·299	0·204	0·095	31·8
Intracoronary lactate	0·567	0·451	NC	NC	0·242	0·471	NC	NC
Intracoronary amrinone	0·575	0·412	NC	NC	0·279	0·274	NC	NC
Intravenous amrinone	0·654	0·610	0·044	6·7	0·256	0·263	−0·007	−2·7
			Pyruvate					
Control	0·031	0·041	−0·010	−32·3	0·039	0·064	−0·025	−64·1
Intracoronary lactate	0·035	0·045	NC	NC	0·040	0·078	NC	NC
Intracoronary amrinone	0·038	0·047	NC	NC	0·044	0·038	NC	NC
Intravenous amrinone	0·035	0·066	−0·031	−88·6	0·048	0·035	0·013	27·1
			Glycerol					
Control	0·143	0·149	−0·006	−4·2	0·143	0·164	−0·021	−14·7
Intracoronary lactate	0·151	0·178	NC	NC	0·130	0·152	NC	NC
Intracoronary amrinone	0·159	0·157	NC	NC	0·136	0·137	NC	NC
Intravenous amrinone	0·183	0·167	0·016	8·7	0·152	0·152	0·000	0·0
			Free fatty acid					
Control	0·73	0·60	0·13	17·8	0·75	0·47	0·28	37·3
Intracoronary lactate	0·85	0·73	NC	NC	0·63	0·48	NC	NC
Intracoronary amrinone	0·75	0·79	NC	NC	0·66	0·51	NC	NC
Intravenous amrinone	0·94	0·63	−0·31	−33·0	0·79	0·63	0·16	20·3
			Glucose					
Control	6·6	6·2	0·4	6·1	6·3	4·5	1·8	28·6
Intracoronary lactate	*	6·5	NC	NC	5·4	4·5	NC	NC
Intracoronary amrinone	7·6	6·4	NC	NC	5·6	4·9	NC	NC
Intravenous amrinone	8·6	6·8	1·8	20·9	5·5	4·9	0·6	10·9

*Broken.
NC, not caltulable.
Conversion: SI to traditional units—Lactate: 1 mmol ≈ 90 mg. Pyruvate: 1 mmol ≈ 88 mg. Glycerol: 1 mmol ≈ 217 mg. Glucose: 1 mmol ≈ 180 mg.

lar function (Table 4). Increases in the arterial concentrations of glycerol, free fatty acid, glucose (Table 4), hydroxybutyrate, and acetoacetate (not tabulated) were seen after intravenous amrinone in both patients. These changes were more pronounced in the patient with poor left ventricular function (glucose concentration being compared with the glucose concentration during the preceding intervention).

Interrelations between variables measured

After intracoronary drug infusions we were unable to detect any relation between coronary sinus amrinone concentrations and haemodynamic or metabolic changes observed. Removal of the one or two patients with the lowest coronary sinus amrinone concentrations does not materially affect mean values or the overall analysis of data.

Patients who received short or long intracoronary infusions received different total doses of the drugs by this route. They all subsequently received the same dose of amrinone (1·5 mg/kg) by the intravenous route. It was thus possible to analyse the haemodynamic effects of intravenous amrinone in these eight patients combined. No relation was found between alterations in contractility and plasma concentrations of amrinone or *N*-acetyl amrinone. As in a previous study[3] we sought a relation between alterations in haemodynamics and metabolic changes after intravenous amrinone. The percentage increase in arterial free fatty acid concentration was linearly related to percentage increase in dP/dt max ($y=7\cdot83+0\cdot38x$, $n=8$, $r=0\cdot64$), although the relation just failed to achieve significance ($0\cdot05<p<0\cdot1$).

An inverse relation existed between control left ventricular ejection fraction (%) and percentage increase in ejection fraction after intravenous amrinone ($y=96\cdot1-1\cdot64x$, $n=8$, $r=0\cdot714$, $p<0\cdot05$). In fact, a relation existed between a number of baseline (control) haemodynamic variables and the response to intravenous amrinone, although not to intracoronary amrinone.

We arbitrarily divided the patients into two groups of four; those with a normalised left ventricular end diastolic volume >200 (range 209–241, mean 222) ml/m^2 and those with a volume index <200 (range 112–183, mean 148) ml/m^2. Those patients with the larger left ventricular end diastolic volumes had lower control mean aortic pressures (57–78 *v* 85–119 mm Hg), higher left ventricular end diastolic pressures (19–27 *v* 4–9 mm Hg), lower dP/dt max (467–780 *v* 913–1154 mm Hg/s), lower left ventricular end systolic pressure/volume indexes (0·26–0·49 *v* 0·63–2·65 mm

Hg/ml/m^2), and lower left ventricular minute work (1·17–3·51 *v* 5·64–9·66 kg m/min) as well as generally lower efficiency (2·1–28·6, mean 10·9 *v* 8·8–35·1, mean 23·7%), cardiac indices (1·1–2·0, mean 1·6 *v* 1·8–3·2, mean 2·6 l/min/m^2), and ejection fractions (6–26, mean 17 *v* 21–52, mean 39%). The two groups had similar resting heart rates, arteriocoronary sinus oxygen differences, coronary sinus flow rates, myocardial oxygen consumptions, and lactate extractions. After intravenous amrinone filling pressures fell by similar amounts in each group, but aortic pressure fell less in the group with the larger left ventricular volumes (5 *v* 22 mm Hg). In the patients with the larger ventricular volumes heart rate was unchanged after amrinone but rose in the other group (range 11–24 (mean 16) beats/min). Cardiac index rose in both groups after intravenous amrinone, but this increase was greater in the group with the larger left ventricular volume in both absolute (0·9–2·2 (mean 1·4) *v* 0·2–1·0 (mean 0·5) l/min) and relative terms (45–122% (mean 89%) *v* 8–56% (mean 23%)). Left ventricular minute work fell after intravenous amrinone in three of the group with the smaller left ventricular volumes, and efficiency was reduced in two, but both variables were improved in each of the four patients with larger left ventricular volumes. In each of the patients with smaller left ventricles, but not in the other group, the left ventricular end systolic pressure/volume index rose appreciably after amrinone. This change, however, was accompanied by a large increase in heart rate in each patient and was not accompanied by consistent alterations in pressure derived contractility indices.

Discussion

Amrinone possesses undoubted positive inotropic properties in myocardium from normal animals and animals with acutely induced cardiac failure.[4, 5] This property is at least partly the result of phosphodiesterase inhibitory activity[21, 22] and partly due to potentiation of the effects of catecholamines on the myocardium.[21] In chronic cardiac failure in myocardium from animals[23] and man[6] the direct positive inotropic effects of amrinone disappear. Even in normal myocardium the concentrations of amrinone required to produce a direct positive inotropic effect are considerably higher than those that can be obtained during long term oral treatment[24–26] because of common, severe, and dose related adverse effects.[25, 27, 28] Amrinone also possesses powerful direct vasodilator properties in animal and human vessels[5, 6, 29] and may also cause systemic catecholamine release in some cases by mechanisms independent of reflex changes resulting from vasodilatation.[3]

This study is an attempt to prevent these peripheral vascular effects and systemic alterations of autonomic or neuroendocrine activity from masking the cardiac effects of amrinone. These cardiac properties could include effects on coronary vessels, cardiac nerves, and myocardial neurotransmitter potentiation, as well as direct effects on myocardial cells themselves.

Intracoronary administration of any drug solution will have effects that are due to partial replacement of coronary perfusing blood by nutrient poor, non-oxygenated solvent as well as those effects due to the pharmacological properties of the drug itself. Consequently, it was necessary to investigate the effect of the solvent (lactate solution) itself in each patient studied. To prevent an order effect the intracoronary infusions were administered in a randomised cross-over manner. The patients and the technicians performing biochemical analysis were unaware of intervention order, and haemodynamic measurements were made by computer. Thus, although the doctors giving the drugs were aware of the order of administration of the infusions (which were different colours) selection and biased interpretation of data were prevented. This technique contrasts appreciably with earlier "titration" studies of the haemodynamic effects of amrinone, in which peak effects and predetermined haemodynamic end points were employed.[7–9] Such studies cannot be used to argue that a drug possesses a particular effect, although the magnitude and time course of that effect can be assessed, provided that the effect has already been adequately shown to be present.

We initially investigated the effect of short intracoronary infusions lasting two minutes. During in vitro experiments exposure of myocardium to amrinone is accompanied by a rapid increase in tension development, which reaches a plateau within two minutes in tissue from both animals[5] and man (unpublished observations). An infusion for two minutes should be an adequate interval for increases in tension to occur if the tissue is responsive and provided that adequate concentrations of amrinone are achieved. To confirm that there were adequate concentrations coronary sinus blood was sampled during the infusions. We also continued observation of haemodynamics after the intracoronary infusion in case late changes occurred.

We administered the drug into the left coronary artery alone, aware that our failure to administer the drug also into the right coronary artery might produce a steal phenomenon or regional dyskinesia. We thought, however, that it would not be justified to cannulate both coronary ostia. The rate of drug infusion was 0·5 mg/min, which we had estimated from mean coronary flows, would produce concentrations of drug in coronary sinus blood in the range of those detected in peripheral blood during long term oral treatment. (We have previously found an incidence of thrombocytopenia greater than 50% in patients receiving long term oral treatment when mean plasma amrinone concentration exceeds 2·5 μg/ml,[26] so we aimed to achieve coronary sinus concentrations of the drug that were lower than this.) We also predicted that unexpected adverse reactions to the intracoronary drug infusions would be unlikely to develop as the concentrations of drug achieved would be lower than those we found in the circulation during the initial five minutes after bolus adminstration of amrinone. These predictions proved accurate.

After this group of six preliminary experiments we intended to proceed to a series of further experiments in which the intracoronary infusions were considerably prolonged in case the occurrence of any inotropic effect of amrinone in vivo is delayed. It was our intention to investigate the effect of long infusions in at least six patients with dilated cardiomyopathy and in as many patients as might prove practical with normal coronary arteries and good left ventricular function who required investigation of myocardial lactate metabolism. We were unable to complete these experiments owing to the manufacturers' action.

In all patients, whether they received long or short intracoronary infusions, the effect of intravenous amrinone was also investigated. This was to confirm that these patients did not respond in an atypical manner to intravenous amrinone, which might for example have explained a surprising response to intracoronary amrinone. In fact the responses of the patients to intravenous amrinone were totally as expected. A reduction in left ventricular filling pressure and an increase in cardiac index occurred in each of the eight patients. The responses of the seven patients with dilated cardiomyopathy to intravenous amrinone were in keeping with our previously published experience.[3 10] The response of the patient with good left ventricular function—that is, appreciable reduction in aortic pressure, increase in heart rate, and impaired myocardial lactate extraction—compared well with that seen in other studies in patients with good left ventricular function.[30 31] In this patient the appreciable increases in contractility indices after intravenous amrinone may have been due to the large increase in heart rate or to catecholamine release as a result of vasodilatation, although a direct positive inotropic effect cannot be excluded. The absence, however, of increased contractility during intracoronary infusion of amrinone in this patient does not support the view that he was able to produce a direct positive inotropic response to amrinone at the concentrations achieved during long term oral treatment.

In this study little evidence was detected that intracoronary amrinone (or the lactate) had any effect on haemodynamics or myocardial metabolism. In particular, it was found that the drug produced no alteration in myocardial contractility during either short or long infusions. After the short intracoronary infusion of amrinone, left ventricular ejection fraction was actually reduced compared with intracoronary lactate. A similar reduction occurred after the long intracoronary infusion of amrinone in the patient with poor left ventricular function but not in the patient with good function. These differences were, however, small and are probably not clinically important even though significant.

Coronary vascular resistance was reduced by the short intracoronary infusions of amrinone in five of the six patients studied and unaltered in the other. Coronary vascular resistance was also reduced in the patient with poor left ventricular function who received the long infusion but increased in the patient with good function. The changes in coronary vascular resistance were detectable after the short amrinone infusion despite an interval of six minutes since the end of the infusion. The reduction in coronary vascular resistance after intracoronary amrinone in patients with poor left ventricular function, although not significant, may be clinically important. These observations are in accord with the reductions in arteriocoronary sinus oxygen difference after intravenous amrinone in this study as well as in similar patients in other studies.[2 3] It suggests that amrinone may have a direct coronary vasodilator effect in patients with poor left ventricular function similar to that described in animal models.[32] It also supports the observations that in vitro the vasodilator effects of amrinone are detectable at lower concentrations than the inotropic effects in both human and animal models.[6]

The increase in coronary vascular resistance seen during the long intracoronary infusion of amrinone in the patient with good left ventricular function is surprising. A possible cause might be that patients with poor left ventricular function have relatively low cardiac stores of catecholamine. Thus coronary vessels in such patients are able to respond by direct vasodilatation to amrinone without a major effect from amrinone induced catecholamine release. In the patient with good left ventricular function intracoronary amrinone should also have tended to produce direct vasodilatation, but this might have been masked by vasoconstriction produced by amrinone induced catecholamine release. Nevertheless, during the intracoronary infusion of amrinone the patient with good left ventricular function showed no evidence of an increase in contractility, which might have been expected if cardiac catecholamine stores were being liberated, and this hypothesis cannot easily be tested.

In the present study we did find evidence to support the view that intravenous amrinone can produce systemic release of catecholamine. As in a previous study, we showed that, although contractility did not increase for the group as a whole after intravenous amrinone, changes in contractility in individual patients were related to metabolic alterations (increased free fatty acid, glycerol, and glucose concentrations), which suggests that they might be the result of catecholamine release.[3 33] Indeed, in the present study the metabolic changes after 1·5 mg/kg intravenous amrinone were identical to those we have previously described in a similar group of patients after the same dose of the intravenous drug.[3]

We also showed that improvements in left ventricular ejection fraction after intravenous amrinone were inversely related to control ejection fraction. The most beneficial changes in other haemodynamic and metabolic variables after the drug were found in the patients with the worst control haemodynamic values. These findings alone would suggest that the effects of intravenous amrinone in cardiac failure are predominately the result of altered loading, even if the effects of intracoronary infusion of amrinone had been less convincing.

Overall these findings agree with our previous observations that in patients with chronic heart failure improvements in haemodynamics after intravenous amrinone are the result of vasodilatation with no evidence of a direct positive inotropic effect.[3 10] In such patients any improvement seen in contractility is likely to be due to the release of catecholamine.[3]

In patients with milder degrees of heart failure an additional direct positive inotropic effect with high concentrations of amrinone cannot be entirely excluded. If present in such a patient, however, this effect coupled with the drug's powerful vasodilator properties might prove disadvantageous because the possible increase in heart rate coupled with excessive reductions in preload, coronary perfusion pressure, and myocardial efficiency may worsen myocardial ischaemia, without the benefit of an appreciable increase in cardiac index.

The intracoronary infusions confirmed that at concentrations of the drug likely to be achieved without adverse effects during long term oral treatment (that is, $<2\cdot5$ μg/ml[26]) amrinone has no positive inotropic effects in human myocardium whether it is from patients with heart failure or nearly normal subjects.

This study highlights the dangers of extrapolating from experiments using very high concentrations of drugs in isolated normal animal myocardium to lower (non-toxic) concentrations in the intact patient, without giving sufficient consideration to additional direct and indirect effects they may have on vessels and the neuroendocrine systems.

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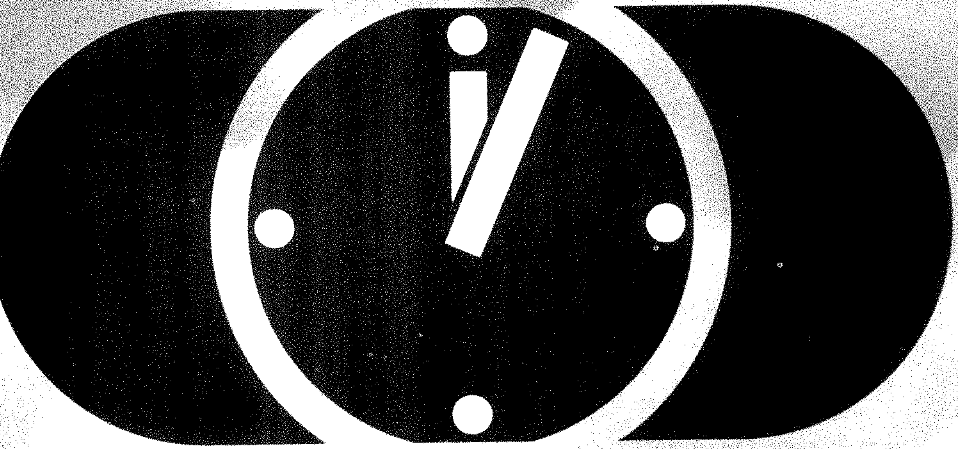

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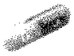
Angina, anxiety, essential tremor, thyrotoxicosis, prophylaxis of migraine.			
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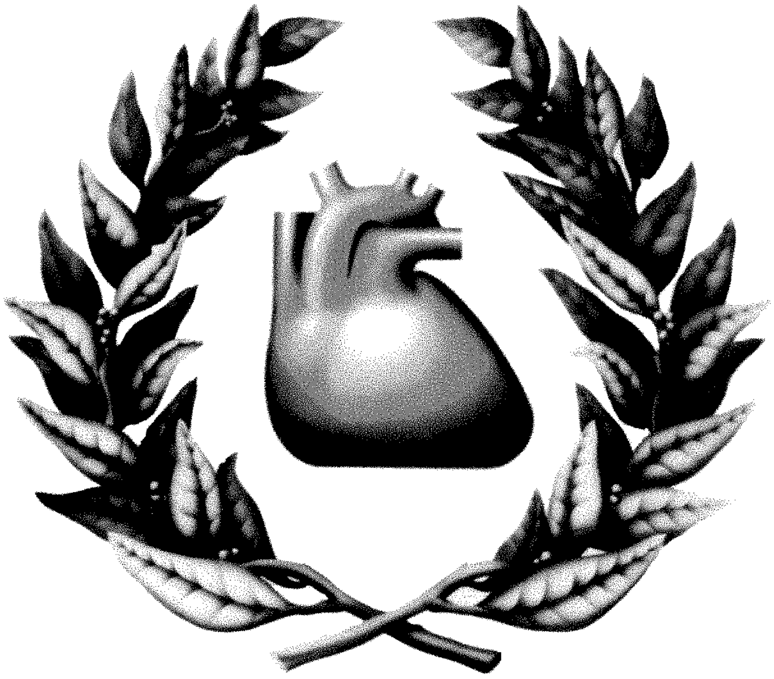

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Br Heart J 1985; **53**: 507–9

Preoperative prediction of prosthesis size using cross sectional echocardiography in patients requiring aortic valve replacement

A MACKAY, M BEEN, E RODRIGUES, J MURCHISON, D P DE BONO

From the Department of Cardiology, Royal Infirmary, Edinburgh

SUMMARY In 43 patients who underwent aortic valve replacement for aortic stenosis with or without regurgitation the accuracy of preoperative left ventricular angiography, parasternal long axis cross sectional echocardiography of left ventricular outflow tract and proximal ascending aorta, and M mode echocardiography of aortic root in predicting aortic root size and thereby prosthesis size was compared. Cross sectional echocardiographic measurements and angiographic measurements of aortic root correlated well with prosthesis size, with over two thirds of the indirect measurements being within 2 mm of prosthesis diameter. M mode echocardiography did not yield useful predictive information. Non-invasive preoperative evaluation of patients likely to require aortic valve replacement may be usefully extended to include aortic root dimensions measured by cross sectional echocardiography.

Surgical replacement of the aortic valve is the definitive treatment of severe aortic stenosis or regurgitation in adults. It is preferable to perform aortic valve replacement electively, even in the absence of severe symptoms, rather than to await decompensation and the less predictable results of emergency surgery. This requires physicians and surgeons to consider all relevant information relating to the advisability, timing, and technique of the procedure. The invasive investigation of patients with aortic stenosis by cardiac catheterisation causes a small but measurable risk, and there is increasing interest in the possibility that adequate preoperative information might be obtained by non-invasive techniques such as echocardiography.[1 2] Echocardiography is useful in the diagnosis of aortic stenosis and regurgitation and, with certain limitations, in assessing their severity.[3–5] It can give an estimate of left ventricular function and identify associated lesions of other valves. Its inability to detect coronary lesions may not be a major handicap in the absence of angina.[2]

We considered that an additional factor, the size of the aortic root, should also be assessed preoperatively. Thus in this study we compared angiographic, M mode echocardiographic, and cross sectional echocardiographic preoperative assessments of aortic root size with the findings at surgery and the size of the valve prosthesis used in 43 patients undergoing aortic valve replacement.

Patients and methods

Forty three patients with aortic stenosis with or without aortic regurgitation who underwent elective aortic valve replacement at this hospital were studied. Thirty were men, 13 women. Their ages at the time of operation ranged from 23 to 72 (mean 57·6) years. In addition to aortic valve replacement four patients also underwent coronary artery bypass graft surgery, four mitral valve replacement, two open mitral valvotomy, and one pericardectomy. Of the aortic valves implanted, 17 were Björk-Shiley prostheses (19–31 mm), 13 Ionescu-Shiley prostheses (21–27 mm), seven Hancock prostheses (21–29 mm), and six Carpentier-Edwards prostheses (23–25 mm). In each case the internal diameter of the aortic annulus was measured with a plastic sizer before the prosthesis was sutured in situ. All prostheses were implanted at the level of the aortic annulus.

As part of their preoperative assessment all

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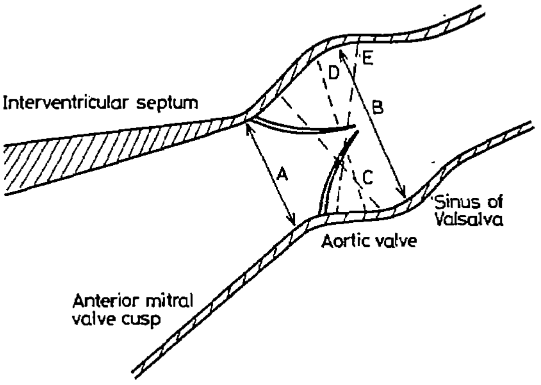

Fig. 1 *Diagram showing basis of echocardiogram measurements on parasternal long axis view of left ventricular outflow tract and proximal ascending aorta. (A) delineates aortic root measurement from luminal surface to luminal surface, and (B) the diameter at the sinus of Valsalva level. (C), (D), and (E) (broken lines) show the possible variations of M mode measurements of aortic root size depending on the siting and angulation of the transducer.*

Table *Correlation of indirectly measured aortic root dimensions with prosthesis valve size*

Technique and measurement	*Correlation coefficient*	*p value*
Cross sectional echocardiogram:		
Root size	0·68	<0·001
Sinus of Valsalva size	0·45	<0·02
M mode echocardiogram:		
Valve level	0·22	>0·05
Left ventricular angiogram:		
Root size	0·62	<0·001
Sinus of Valsalva size	0·58	<0·001

patients underwent M mode and cross sectional echocardiography and cardiac catheterisation. Echocardiography was performed using an Irex System III real time phased array imaging system (Irex Medical Systems, New Jersey, USA) with patients lying supine or in the left semilateral position. A 2·5 MHz transducer was used to obtain cross sectional parasternal long axis views of the left ventricle, left ventricular outflow tract, aortic valve, and proximal ascending aorta, as well as short axis views of the left ventricle and aortic root. Measurements were made on the long axis recordings. A 2·25 MHz transducer was used to obtain M mode recordings of the aortic root. In some patients calcification in the region of the aortic root and valve made cross sectional (n=4) or M mode (n=14) records unsuitable for quantitative analysis. Left ventricular angiography in the 30° right anterior oblique projection was performed by standard techniques using Urografin 370. Angiograms were recorded in all except eight patients, in whom a severely disorganised valve could not be crossed.

Four observers participated in the study. Each record was measured in triplicate by two observers independently. Measurements were made on cross sectional echocardiograms and left ventricular angiograms according to a predetermined protocol. Aortic root size (A) (Fig. 1) was measured from luminal surface to luminal surface, from the point where interventricular septum became anterior aortic root to the point where anterior mitral valve cusp became posterior aortic root. Further measurements (B) (Fig. 1) were taken parallel to the root measurements at the point of maximum aortic diameter in the region of the sinuses of Valsalva, again from luminal surface to luminal surface. M mode measurements were taken at the aortic valve level from luminal surface to luminal surface at the end of ventricular diastole.

Linear regression analysis was used to compare indirect measurements of aortic size with the dimensions of the prosthetic valves at subsequent surgery.

Results

There was good correlation (Table) between the size of the aortic annulus, as assessed at surgery and reflected in prosthesis size, and the angiographic or cross sectional echocardiographic estimates of aortic root size (Fig. 2) (coefficients of correlation 0·62, 0·68 respectively). Indirect measurements of root size tended to underestimate prosthesis size, but the differences were not large. Seventy two per cent of cross sectional echocardiogram measurements (n=39) and 70% of angiographic measurements (n=35) were within 2 mm of the prosthesis size used at operation. Cross sectional echocardiography also detected two

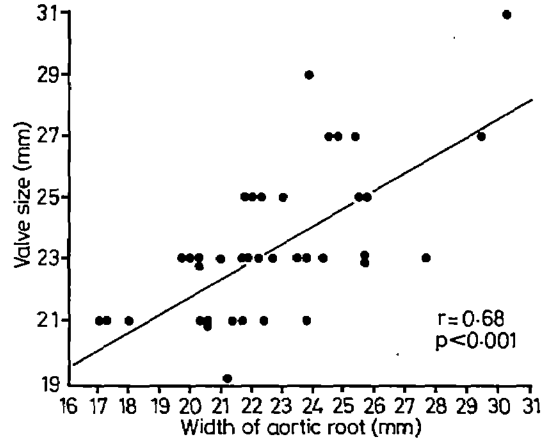

Fig. 2 *Correlation of cross sectional echo measurements of aortic root size with prosthesis dimensions at subsequent surgery.* $y=0{\cdot}57x+10{\cdot}4$; $n=39$; $r=0{\cdot}68$; $p<0{\cdot}001$.

cases of subvalvar aortic stenosis associated with valvar stenosis.

There was little variation between the observations of pairs of observers reporting both cross sectional echocardiographic (coefficient of correlation 0·94, 0·91) and angiographic (coefficient of correlation 0·89, 0·92) data.

M mode assessments were less closely correlated with prosthesis size, only 42% of M mode meaasurements lying within 5 mm of the prosthesis size used.

Discussion

The optimum choice of aortic valve prosthesis is still controversial. Mechanical prostheses have a longer track record than xenografts or pericardial tissue valves, particularly in young patients, but are haemodynamically less efficient. Use of the smaller size of mechanical prosthesis may be associated with a persisting left ventricular outflow gradient after surgery, so called patient-prosthesis mismatch.[6] Techniques are available to increase aortic root diameter by inserting a gusset,[7 8] but they increase operation time and the risk of haemorrhagic complications. It is also possible to insert a valve in a supra-annular position, when special care is needed not to obstruct the coronary ostia. Preoperative knowledge of the size of the aortic root will be a factor that will help to predict the requirements of individual patients. In turn, knowledge of the type of valve or procedure likely to be needed may influence the timing of surgery. It is also important for the surgeon to know of any subvalvar aortic obstruction since failure to relieve this will negate the effects of valve replacement. Finally the extent of calcification in the aortic valve ring and its possible extension into the crus cordis may be relevant information in predicting the ease and safety of valve replacement.

The present study indicates that real time cross sectional echocardiography and angiography correlate well in their estimates of aortic root size and are equally effective in predicting the size of the prosthesis that may be used but that M mode echocardiography is less effective. It is recognised that assessment of aortic root size at surgery using a sizer is prone to inaccuracy, but, nevertheless, it is a practical procedure related to the size of prosthesis to be implanted. A further potential source of error might be supra-annular positioning of prostheses, but in this study in no instance did the surgeon record implantation of a prosthesis at a site other than that of the aortic annulus. Our echocardiographic findings are in agreement with those of a recent study in which a small number of patients with aortic stenosis was studied,[9] while the value of invasive investigation by angiography in determining aortic root size has been previously demonstrated.[10]

Cross sectional echocardiography is also effective in providing information about subvalvar stenosis and calcification of the crus cordis, but technical factors related to the shape of the chest and the disposition of the heart may prevent satisfactory recordings being obtained in all patients.

M mode echocardiography has been regarded as a reliable technique for measuring aortic root diameter in normal subjects or those with non-calcific aortic valve disease.[11] Its lack of efficacy in the present study largely reflects the difficulty in orientating the transducer reliably (Fig. 1) in the presence of multiple strong echoes from calcific material and in deciding the precise boundaries of the aortic root.[12]

In summary, we have found that either angiographic or cross sectional echocardiographic measurements of aortic root size can help to predict the size of prosthesis that can be accommodated, and we suggest that their measurement should be part of the routine assessment of patients for aortic valve replacement. The echocardiographic measurements may be particularly useful when valve replacement is undertaken without prior angiography, a course which has been increasingly supported for patients without angina.[2]

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Mechanism of late failure of the Alvarez disc valve prosthesis

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SUMMARY An Alvarez disc valve prosthesis had been implanted in the mitral and tricuspid positions in 15 patients between 1964 and 1967 in this hospital. Of these 15 patients, only three survived longer than 10 years, all three dying unexpectedly between 16 and 18 years postoperatively. Two deaths were a direct result of disruption of the Alvarez prosthesis. The third patient was not examined at necropsy, but in retrospect the history was highly suggestive of valve malfunction. Cross sectional and pulsed Doppler echocardiography made valuable contributions to the diagnosis in both cases of valve disruption and, when available, should be part of the primary investigation of suspected prosthetic heart valve failure.

The Alvarez valve prosthesis is liable to erosive wear which may cause late detachment of the disc from the valve ring with abrupt and catastrophic haemodynamic consequences.

The Alvarez disc valve prosthesis, made of polypropylene, was developed at the Experimental Surgical Unit at the Postgraduate Medical School, London, in the early 1960s.[1] It was first introduced into clinical use in 1964. Fifteen of these prostheses were implanted at Killingbeck Hospital between 1964 and 1967,[2] seven in the mitral position and eight in the tricuspid position. One valve in the tricuspid position was replaced by a different prosthesis after the development of paraprosthetic leak, and two patients died perioperatively. Of the 12 remaining patients, nine died within five years of operation (without evidence of valve failure) and three survived longer than 10 years. One of these three patients died after a 48 hour pyrexial illness in 1983 and the other two died in 1984 as a direct result of mechanical failure of the Alvarez prosthesis. In these two patients the valve disc had become detached from the valve ring owing to erosion of the polypropylene disc struts.

Use of the Alvarez prosthesis was abandoned at this hospital in 1967 because of the high incidence (62·1%) of thromboembolic complications reported when the prosthesis was used in the mitral position.[3]

Patients and methods

CASE REPORTS

Case 1

A 61 year old man was admitted for investigation of jaundice and hepatomegaly. Eighteen years previously he had undergone aortic, mitral, and tricuspid valve replacements for rheumatic valve disease with a No 10 Starr-Edwards, a No 3 Starr-Edwards, and a 2·25 cm Alvarez prosthesis respectively. Initial investigation suggested cholelithiasis. During induction of anaesthesia before cholecystectomy he suffered a cardiac arrest, from which he made a good recovery, but after this he found his exercise tolerance had deteriorated. He was readmitted at a later date, and endoscopic retrograde cannulation of the pancreatic duct and a sphincterotomy were performed under antibiotic cover. After this procedure he became pyrexial and increasingly icteric, with signs of worsening right heart failure and a low cardiac output. The chest radiograph showed gross cardiomegaly and the electrocardiogram widespread repolarisation changes. Echocardiography showed moderately impaired left ventricular function, with a dilated and poorly contracting right ventricle. The aortic and mitral Starr-Edwards prosthetic valves appeared normal, but the tricuspid valve disc was not visible. Pulsed Doppler echocardiography showed very high blood velocities

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across the tricuspid valve (Fig. 1a) and no prosthetic valve clicks were detected, strongly suggesting valve malfunction. Despite intensive supportive therapy, the patient died two days later.

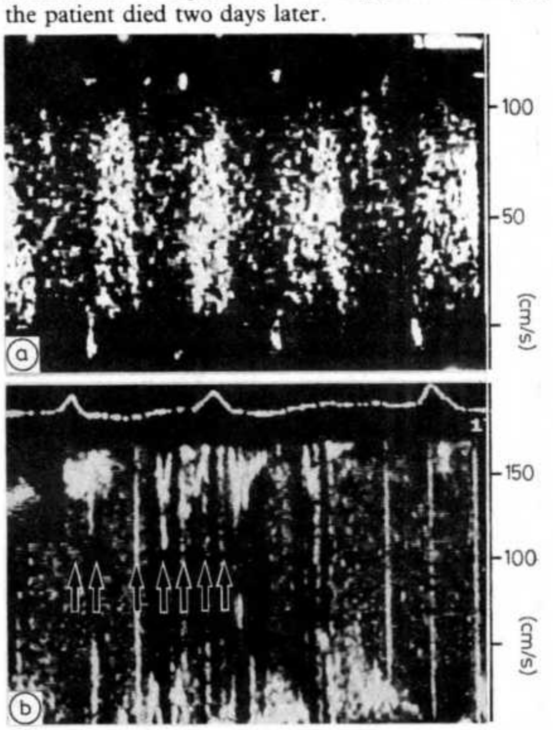

Fig. 1 *Pulsed Doppler echocardiograms of (a) right ventricular inflow in case 1 showing abnormally increased peak velocity with aliasing above 100 cm/s, approximately twice the normal value; and (b) left ventricular inflow in case 2 showing a bizarre pattern with multiple abnormal velocity waves (arrowed) due to the chaotic motion of the valve disc within the left ventricle.*

At necropsy the heart was found to be considerably enlarged. When the right lung was removed the disc of the Alvarez tricuspid valve was found to lie in the right pulmonary artery. The valve ring had remained in the tricuspid position. The mitral and aortic prostheses appeared to be normal. Closer examination of the Alvarez prosthesis showed considerable areas of wear (Fig. 2), particularly of the disc struts, which had been worn down to a shark's tooth appearance and were considerably diminished in size, allowing the disc to displace freely from its ring. The ring itself was also worn in the area of contact with the strut. There were multiple pigment stones in the gall bladder, and the liver showed severe cardiac cirrhosis.

Case 2

A 56 year old woman suffered a cardiac arrest on the way to hospital, having become acutely and severely dyspnoeic. A prolonged resuscitation procedure resulted in restoration of cardiac output followed by status epilepticus. Sixteen years earlier she had undergone mitral valve replacement with a 2·25 cm Alvarez prosthesis for rheumatic valve disease.

Examination of the cardiovascular system showed pronounced hypotension, a hyperdynamic left ventricular impulse, loud prosthetic valve clicks, and a soft systolic murmur audible at the left sternal edge. The chest radiograph showed gross cardiomegaly with pulmonary oedema and the electrocardiogram a bizarre cardiac rhythm. Echocardiography showed a well contracting, hypertrophied left ventricle which contained a freely moving echo dense object (Fig. 3). This appeared to merge with the mitral valve ring in systole and to move rapidly to the apex of the ventricle in diastole. Doppler echocardiography produced high pitched squeaking sounds in place of the usual prosthetic valve clicks and showed a bizarre flow velocity pattern in the left ventricular inflow tract (Fig. 1b). A diagnosis of mechanical prosthetic valve failure was made, but the patient failed to show any sign of cerebral recovery. Her condition rapidly deteriorated and she died 24 hours later.

At necropsy the valve disc was found to be lying in the valve ring but with the struts in an abnormal position. When the heart was lifted up the disc fell freely into the left ventricular cavity, returning to its previous position when the heart was inverted. As in the patient in case 1 the prosthesis showed signs of advanced erosion of the disc struts, which again were sharpened and greatly reduced in size, allowing the disc to move freely in and out of the valve ring. The disc also showed considerable wear at its point of diastolic contact with the ring, which could well have produced prosthetic leakage. The valve ring itself was worn in a similar fashion to that in the first patient (case 1) in the area of contact with the disc struts (Fig. 4).

Case 3

A 44 year old man, who had undergone mitral (Starr-Edwards) and tricuspid (Alvarez) valve replacement in 1967, was admitted to his local hospital having become suddenly unwell with diarrhoea, pyrexia, and confusion. He was found to have a severely raised jugular venous pressure and Gram positive bacteraemia. Despite an initial apparent improvement after antibiotic treatment, he developed disseminated intravascular coagulopathy and suffered a cardiac arrest from which he did not recover. Unfortunately, a necropsy was not performed. The short history preceding death had similarities with that in the patient in case 1, and retrospective review of the case records showed that the pronounced increase in jugular venous pressure had not been present at a recent out-

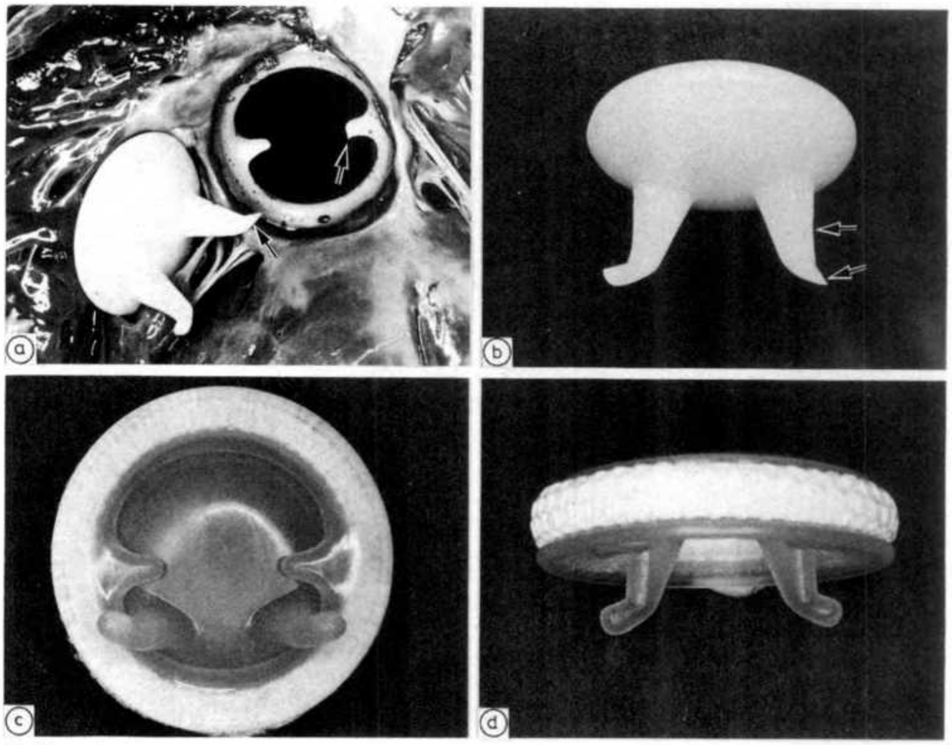

Fig. 2 *(a) The valve disc and ring in case 1 showing the areas of wear (arrowed), which allowed the disc to displace. The ring is worn at the site of contact with the retaining struts of the disc, which are themselves badly eroded. (b) The areas of disc wear are seen more clearly in profile. The extent of wear is emphasised by comparison with an unused Alvarez prosthesis ((c) and (d)).*

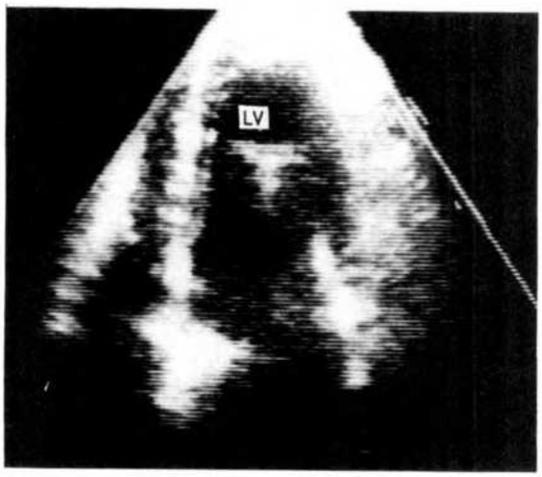

Fig. 3 *Cross sectional echocardiogram in the apical four chamber view in case 2 showing the echo dense valve disc lying within the left ventricular cavity (LV).*

patient assessment. Without postmortem information there can be no proof of prosthetic valve disruption causing this patient's unexpected death, but there is a strong possibility that this was the case.

Discussion

Diagnosis of prosthetic valve mechanical failure may be difficult. Muffled or absent prosthetic clicks may be a valuable indicator of valve malfunction,[4-6] and particular emphasis has been placed on the importance of the opening sound of the Starr-Edwards prosthesis in the aortic position.[7] Phonocardiography may be useful in detecting more subtle changes in prosthetic sounds.[8] Echocardiographic assessment of prosthetic ball[9] or disc[10] motion may provide useful information, particularly in valve obstruction, and assessment of left ventricular function can help to exclude poor myocardial contraction as a cause of diminished click volume.[11] Nevertheless, even when these techniques together with fluoroscopic screening of the valve are used, discernible abnormalities may occur only when damage to the prosthesis is well advanced.[7 12]

Our second patient (case 2) is the first reported in whom the valve clicks were increased rather than

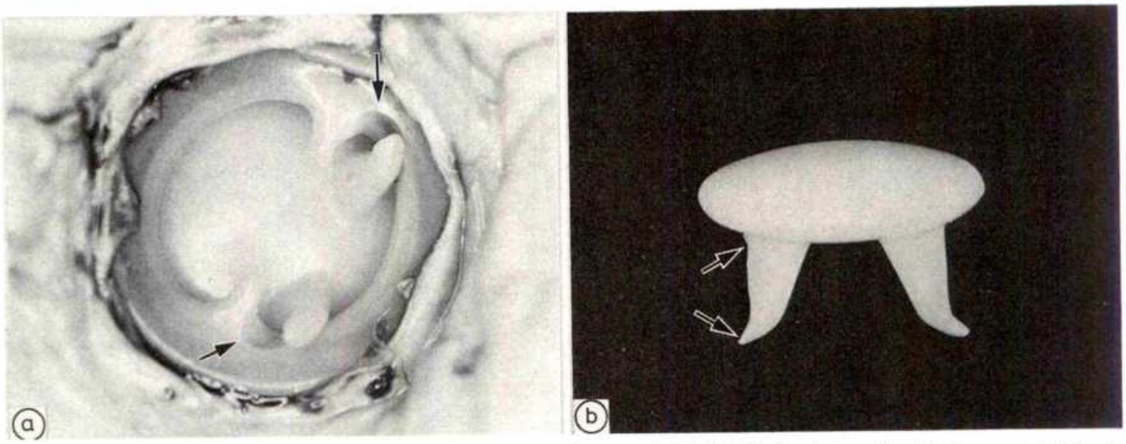

Fig. 4 *Morphological appearance of the prosthetic valve removed from case 2. (a) The disc has been replaced in its correct position in the valve ring. The ring itself has worn (arrows) considerably more than that in case 1. (b) shows the extent of strut erosion (arrows).*

diminished despite complete separation of the disc from the valve ring. This was undoubtedly due to the continued movement of the disc within the left ventricular cavity. The disc struts, which are an integral part of the disc, probably prevented it from being ejected from the heart. Valve clicks were, however, absent in two reported cases in which the Björk-Shiley discs remained within the left ventricle[5] and the left atrium[13] after valve disruption, despite the discs lying free within the heart cavities at the time of emergency reoperation.

In two of our patients (cases 1 and 2) cross sectional and pulsed Doppler echocardiography made important contributions to the diagnosis. Doppler may provide useful information on prosthetic valve obstruction and paraprosthetic leak in aortic,[14] mitral,[15 16] and tricuspid[17] positions; our first two cases indicate that it may also be invaluable in the diagnosis of valve disruption. We now regard both these investigations as an essential part of evaluation of prosthetic valve malfunction.

There can be no doubt that immediate valve replacement is the only effective treatment for valve disruption.[4–7 11 12] Neither of our first two patients underwent repeat surgery as one (case 1) was septicaemic and in hepatic and renal failure and the diagnosis was uncertain; the other (case 2) failed to show evidence of recovery of cerebral function after her prolonged resuscitation procedure.

The most common cause of embolisation of prosthetic valve discs is fracture of either the disc struts or the disc itself. Both major strut[4 13] and minor strut[5 6 18] fracture of the Björk-Shiley prosthesis with resulting disc embolisation have been reported, but there was little evidence of disc wear in these cases. Even the current pyrolitic carbon discs may fracture,[19] and signs of very early disc burnishing have been reported in valves even after a few hours in patients who died on the operating table.[20] Nevertheless, the clinical performance of the Björk-Shiley valve has been excellent overall, and Clark *et al* found only minimal signs of valve wear after 973 million cycles of accelerated fatigue testing.[21] Titanium valve struts may also be liable to wear in the DeBakey ball valve.[22] In contrast, Alvarez valve disruption in two of our patients (cases 1 and 2) occurred after approximately 600 million cycles, by which time very advanced wear was apparent.

Plastics might logically be expected to undergo more wear than harder materials such as pyrolite, and published reports support this. Severe wear of the Teflon disc of a Wada-Cutter valve may also occur with remarkably similar findings to those in our cases.[23] The Beall valve Teflon disc has also been shown to undergo excessive wear in both its early and later strengthened forms.[24 25]

CONCLUSIONS

The Alvarez disc valve is subject to severe wear, which may lead to valve disruption after approximately five to six hundred million cardiac cycles. We strongly recommend that any patient with an Alvarez prosthesis be offered valve replacement.

Plastics such as polypropylene and Teflon show signs of wear much earlier than pyrolite and titanium and are therefore unsuitable materials for the construction of prosthetic valve discs in their present forms. Prolonged in vitro accelerated fatigue testing may be necessary before serious wear is detected.

The early diagnosis of prosthetic valve disruption is essential if the patient is to survive and may be greatly assisted by cross sectional and pulsed Doppler echocardiography.

We thank Mr Duncan Walker for permission to report case 2, Dr B Lynch for performing the postmortem examination of case 1, and Dr S Apparacio for performing the postmortem examination of case 2.

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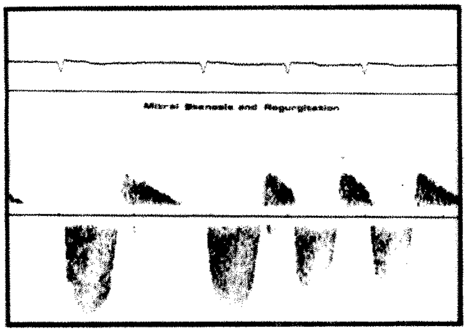

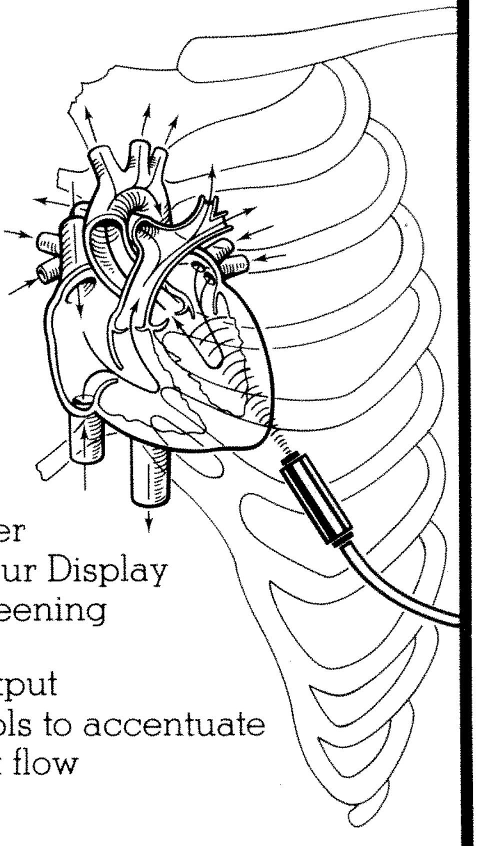

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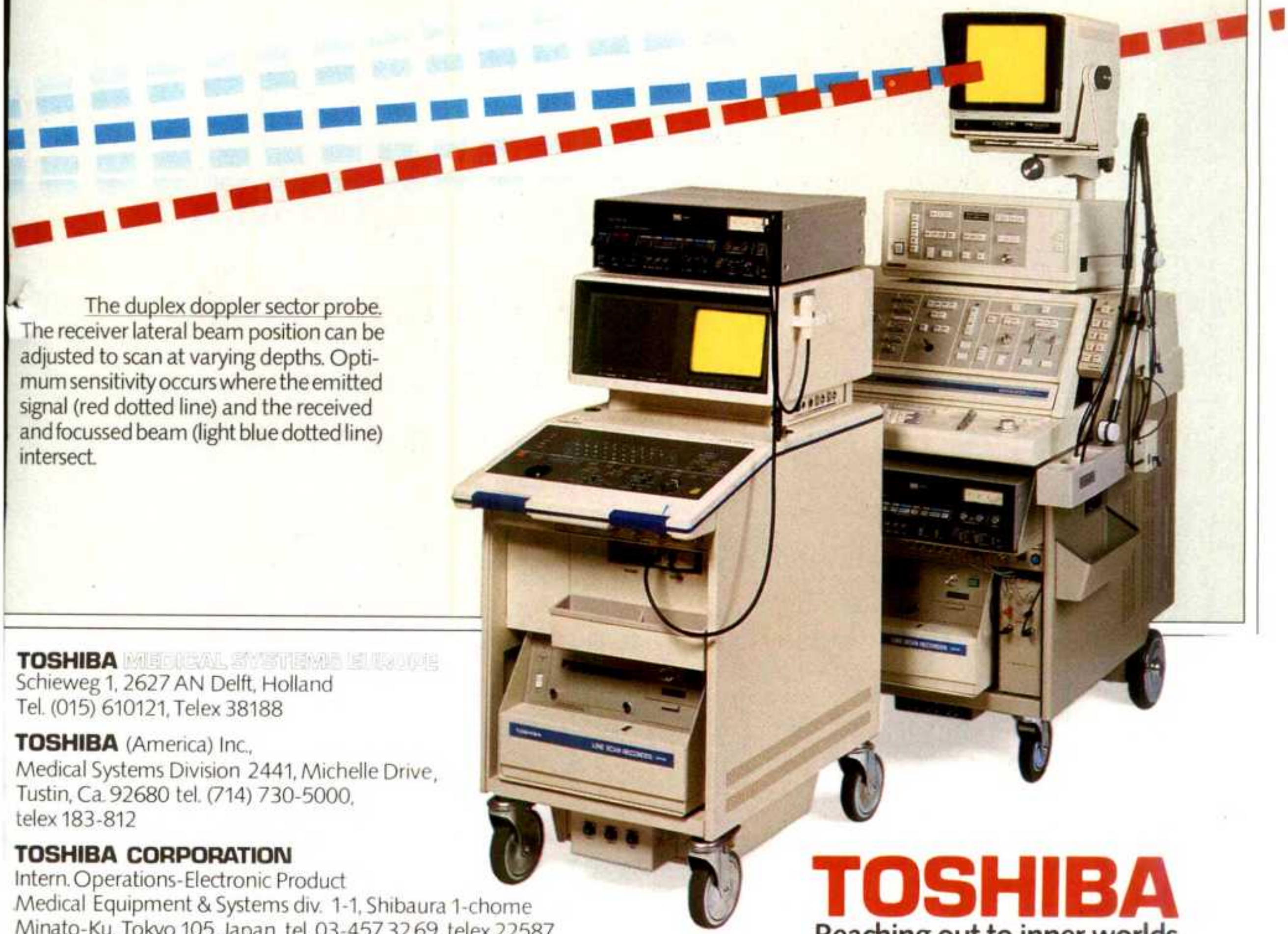

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Double inlet ventricle
Lung biopsy findings and implications for management

ERNESTO JUANEDA, SHEILA G HAWORTH

From the Department of Paediatric Cardiology, Institute of Child Health, London

SUMMARY The lung was biopsied in 20 children with double inlet ventricle and pulmonary hypertension aged 2 months to 14 years. Eleven patients had two patent atrioventricular valves, three atresia of the right valve, and six hypoplasia of the left valve. Severe pulmonary arterial medial hypertrophy occurred in the nine children <1 year of age. The findings did not suggest a period of normality after birth when the pulmonary artery might have been banded most effectively. Of the 11 older patients, eight had medial hypertrophy and three intimal proliferation with medial atrophy. Six patients with medial hypertrophy had some reduction in pulmonary arterial pressure after banding.

It is recommended that the pulmonary artery be banded as early as possible, and rebanded early if a satisfactory result is not obtained, particularly in patients destined for a Fontan-Kreutzer procedure. Early atrial septectomy should reduce the arterial and venous abnormalities seen in left atrioventricular valve hypoplasia.

The development of pulmonary vascular disease in patients with double inlet ventricle and an excessive pulmonary blood flow is thought to be similar to that seen in patients with a large isolated ventricular septal defect. Pulmonary vascular resistance is high after birth, reaches a nadir at six months, and is high in older children.[1] Banding of the pulmonary artery is recommended to prevent the development of pulmonary vascular obstructive disease and to allow regression of any arterial medial hypertrophy that is already present. Recent advances in surgical technique, however, demand a more precise understanding of the development of pulmonary vascular disease in this condition. A double inlet ventricle may be repaired by septation of the main chamber or by connecting the right atrium to the pulmonary artery with, if necessary, closure of the right atrioventricular valve, the Fontan-Kreutzer procedure.[2 3] The risk of septation is increased when pulmonary vascular resistance is raised, although the severity of pulmonary vascular disease that characterises the increase in mortality is not known.[4] There are two reports of mortality being significantly higher after a Fontan-Kreutzer procedure in patients with a "single ventricle" than in those with classical tricuspid atresia, without there being an obvious explanation.[4 5]

A recent small study suggested that the risk of a Fontan procedure is higher in patients with a double inlet ventricle and an increase in pulmonary blood flow than in those with classical tricuspid atresia and hypoperfusion because pulmonary vascular smooth muscle can be increased in such patients even when the pulmonary artery has been banded and the criteria for a Fontan operation have been largely fulfilled.[6] These observations suggest that it is crucial to band the pulmonary artery at an age when there is the greatest likelihood of achieving a normal pulmonary vascular bed subsequently. We have therefore studied the pulmonary vascular changes in lung biopsy specimens from 20 patients with a double inlet ventricle, usually before the pulmonary artery was banded. Eleven patients had two patent atrioventricular valves, three atresia of the right valve, and six hypoplasia of the left atrioventricular valve.

Patients and methods

The 20 patients were aged between 2 months and 14·5 years. Nine were boys and 11 girls. Table 1 shows the clinical and haemodynamic data. Eighty per cent of

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Table 1 *Double inlet ventricle in patients with two patent atrioventricular valves and in those with atresia of the right or left atrioventricular valve*

Case No	*Additional diagnosis*	*Age at biopsy*	*Cardiac catheterisation results at lung biopsy*						*Outcome*
			PAP (mm Hg)	*SAP (mm Hg)*	*Qp:Qs*	*Rp:Rs*	*Rpa (units m²)*	*% Oxygen saturation*	
				Patent atrioventricular valves					
1	TGA	3 mnth	75/30	75/40	2·8	0·36	5·4	88	PAB (twice), alive
2	Dextrocardia	5 mnth	66/10	70/40	—	—	1·8	—	Died during PAB
3	TGA, PDA	5·5 mnth	80/40	80/50	1	0·90	10·4	75	Alive*
4	PDA	7 mnth	60/25	70/35	8·2	0·10	2·1	—	Alive*
5	TGA	8 mnth	80/30	80/50	—	—	—	67	Alive*
6	PS	8 mnth	45/?	80/?	—	—	—	—	Died during Fontan procedure, aged 7·5 yr
7	—	1·5 yr	90/45	90/45	2·4	0·35	3·4	87	PAB (twice), alive
8	—	1·9 yr	70/35	70/40	0·9	1·00	13·3	69	Blalock-Hanlon septectomy performed at time of lung biopsy, alive*
9	TGA, PS	3·5 yr	46/28	88/?	2·5	—	—	—	Alive*
10	—	5 yr	90/50	90/50	—	—	—	—	Alive*
11	—	7·5 yr	68/42	75/54	4·5	0·15	2·7	89	Died during Fontan procedure, aged 8 yr
				Atresia of right atrioventricular valve					
12	TGA	6 mnth	85/40	100/70	2·1	0·32	11·0	77	Alive*
13	—	1·9 yr	100/40	100/60	1·8	1·00	13·0	68	Died during PAB
14	—	5·3 yr	80/40	85/40	4·3	—	3·0	95	Alive*
				Hypoplasia of left atrioventricular valve					
15	—	2 mnth	70/?	75/45	—	—	—	—	Blalock-Hanlon septectomy performed at time of lung biopsy. Died during Fontan procedure, aged 5 yr
16	Coarctation†	2·5 mnth	70/35	70/35	3·4	0·2	5·2	91	Died during Blalock-Hanlon septectomy
17	—	3·7 yr	28/15	86/52	—	—	—	72	PAB at 9 mnth, alive
18	—	4·9 yr	85/65	85/50	0·7	1·8	20·5	77	Alive*
19	—	8·8 yr	75/40	88/58	0·8	0·9	16·0	75	Blalock-Hanlon septectomy performed at time of lung biopsy, alive*
20	CHB	14·5 yr	103/39	98/67	0·9	—	9·0	88	Blalock-Hanlon septectomy performed at time of lung biopsy, alive*

*Having had banding of the pulmonary artery.
†Mean pressure gradient 10 mm Hg.
CHB, complete heart block; PAB, pulmonary artery band; PAP, pulmonary arterial pressure; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; Qp:Qs, pulmonary to systemic blood flow ratio; Rpa, pulmonary arteriolar resistance; Rp:Rs, pulmonary to systemic resistance ratio; SAP, systemic artery pressure; TGA, transposition of great arteries.

patients were on or below the twenty fifth centile for weight, 45% being below the third centile. All the patients were or had been in cardiac failure. The chest radiograph showed cardiac enlargement and an increase in pulmonary vascular markings in all patients except one (case 6), who had mild pulmonary stenosis. Nineteen patients had pulmonary hypertension (Table 1). The pulmonary arteriolar resistance was 1·8–5·4 units m² in seven patients and at least 9 units m² in seven, three with and four without left atrioventricular valve hypoplasia. In 18 patients the lung was biopsied at thoracotomy for banding the pulmonary artery or electively in unbanded patients to help decide the management of the case, or in one patient (case 20) at the time of insertion of a pacemaker and a Blalock-Hanlon operation. In one other patient (case 16) lung tissue was obtained when the patient died immediately after atrial septectomy. Only in one patient (case 17) had the pulmonary artery been banded before the lung was biopsied. The time interval between cardiac catheterisation and biopsy was short, less than one month in 17 cases and four months in two cases. To date 14 patients are alive and well without corrective surgery, the pulmonary artery having been banded in all except one (case 20). Two children died immediately after the pulmonary artery was banded, one (case 16) after atrial septectomy and three immediately after a Fontan proce-

Table 2 *Haemodynamic effect of banding the pulmonary artery*

Case No	*Age at biopsy and banding*	*Pre-banding mean PAP:SAP ratio*	*Time interval*	*Post-banding mean PAP:SAP ratio*	*Rpa*
1	3 mnth	0·9	2 mnth	0·5	3·1
6	7 mnth	0·8	3 yr	0·2	—
7	1·5 yr	1·0	2 yr	0·6‡	—
12	7 mnth	0·7	6 mnth	0·5	3·6
15	2 mnth*	—	9 mnth	0·4	4·7
17	9 mnth†	—	2·8 yr	0·3	—
19	8·8 yr*	0·7	6 mnth	0·4	3·1

*Blalock-Hanlon operation.
†Banded before biopsy performed.
‡One year after a second banding operation the mean pressure ratio was 0·2.
PAP, pulmonary artery pressure; SAP, systemic artery pressure; Rpa, pulmonary arteriolar resistance.

dure. The time interval between the pulmonary artery banding and the Fontan operation was six years in case 6, six months in case 11, and four years in case 15.

Six patients in whom the lung was biopsied and the pulmonary artery banded underwent cardiac catheterisation two months to three years later, and all showed a reduction in pulmonary arterial pressure (Table 2).

PATHOLOGICAL STUDIES

The lung biopsy specimens were taken when the lung was at least partially inflated and were fixed with the small airways and alveoli inflated. Paraffin embedded sections, 4 μm thick, were stained with haematoxylin and eosin, with Miller's elastic stain counter stained with Van Giesen's stain, and with Perl's stain for iron. In each biopsy specimen pulmonary vascular structure was analysed using quantitative morphometric techniques and the findings compared with the normal for age.[7 8] Pulmonary arterial muscularity was assessed by determining the mean percentage arterial medial thickness of arteries in different size ranges. The proportion of muscular, partially muscular, and non-muscular arteries accompanying terminal and respiratory bronchioli and alveolar ducts was also assessed in order to discover if muscle had differentiated in more peripheral arteries than is normal for age. In each biopsy specimen the size of the intra-acinar (respiratory unit) arteries was determined by measuring the external diameter of all arteries seen accompanying terminal and respiratory bronchioli and alveolar ducts and estimating the mean external diameter at each airway level. The number of arteries was estimated by counting the number of alveoli and arteries within as many different microscopic fields as possible and calculating the mean ratio of alveoli to arteries.

In each case the percentage arterial medial thickness in arteries of different size ranges was compared with the normal for age using two way non-orthogonal analysis of variance. Student's unpaired *t* test was used when comparing arterial size.

Results

All 20 patients showed a significant increase in mean percentage arterial medial thickness (Figure) ($p<0{\cdot}0001$). In the 11 patients (cases 1–11) with two atrioventricular valves mean percentage arterial medial thickness was greatest in the seven without either pulmonary stenosis or atrophy of the pulmonary arterial walls. The three patients (cases 12–14)

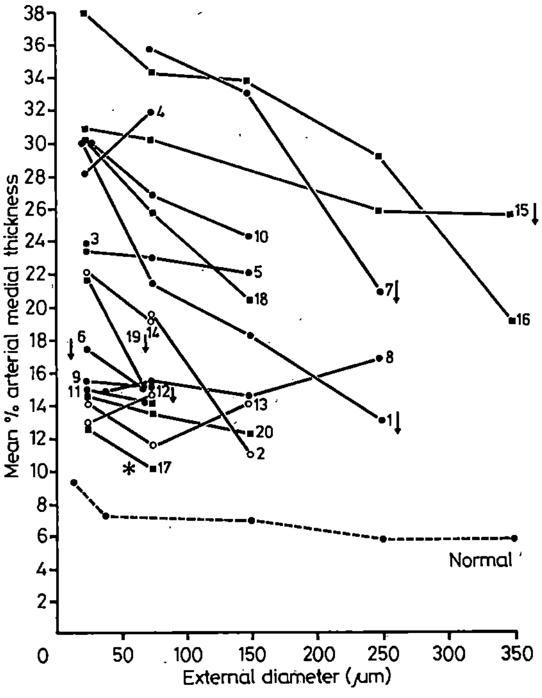

Figure *Mean percentage pulmonary arterial medial thickness related to external diameter (µm) in lung biopsy specimens taken from 20 patients with double inlet ventricle compared with normal. Numbers indicate case numbers. Arrows indicate those patients who subsequently had a reduction in pulmonary arterial pressure after banding. *The only patient to have undergone banding before the lung was biopsied.*

with atresia of the right atrioventricular valve tended to show a less pronounced increase in muscularity than the 11 patients without. In the six patients (cases 15–20) with left atrioventricular valve hypoplasia muscularity was similar to that seen in cases 1–11 except for the banded case (case 17) in which muscularity was relatively low. In each of the 20 patients the proportion of entirely muscularised arteries at each level was greater than expected for the age of the child, indicating that muscle had differentiated in more peripheral arteries than normal.

Circumferential intimal proliferation tended to occur in the older patients aged ≥1·9 years and was found in the preacinar or the intra-acinar arteries or both of cases 8–11, 14, 18, and 20. The most severe intimal changes were present in case 8, and in this case and in cases 11 and 18 the media of alveolar duct and alveolar wall arteries was atrophied distal to thick walled arterial segments containing intimal proliferation. Mild intimal proliferation was also present in the alveolar duct arteries of three younger patients (cases 3, 4, and 6).

In 14 of the 20 cases the preacinar veins were abnormally thick walled, and the small veins had developed an external elastic lamina and were "arterialised." The veins in five patients (cases 9, 10, and 18–20) showed intimal fibrosis. The lungs of the three oldest patients with left atrioventricular valve hypoplasia (cases 18–20) had the greatest increase in vein wall thickness and intimal fibrosis.

The mean external diameter of arteries accompanying respiratory bronchiolar and alveolar duct arteries was normal in five cases, significantly increased at one or both of those positions in 12 ($p<0·01$), and reduced in three (cases 18–20), the reduction being statistically significant in alveolar duct arteries ($p<0·001$). The mean alveolar to arterial ratio was normal for age in 14 of the 18 patients in whom it could be determined accurately. In the four abnormal cases (cases 8, 10, 17, and 18) the mean ratio was 12·4–13·8 above the normal mean level for age (8·4–10·9) but within 1 standard deviation of the normal mean value, suggesting that in no case was there a significant reduction in the number of arteries per unit area of lung tissue.

Discussion

In these 20 patients with double inlet ventricle there was a striking increase in pulmonary vascular smooth muscle that was rather less in those with atresia of the right atrioventricular valve than in those with two patent valves or left atrioventricular valve hypoplasia. The intra-acinar arteries were normal or even increased in size for age, and the number of intra-acinar arteries per unit area of lung was within normal limits. Only three of the 20 patients showed significant obstructive pulmonary vascular disease, all were at least 1·9 years old and one had an obstructed left atrioventricular valve. Severe medial hypertrophy with little if any intimal proliferation was seen in patients <1 year of age. Excluding cases with right atrioventricular valve atresia, the increase in muscularity in patients with double inlet ventricle and an increased pulmonary blood flow was greater than is usually seen in ventricular septal defect during the first year of life, although like patients with a ventricular septal defect intimal proliferation was uncommon at this age.

Six patients whose lung biopsy specimens showed severe pulmonary arterial medial hypertrophy were recatheterised after banding the pulmonary artery, and it was reassuring to find that all had a reduction in pulmonary arterial pressure. Two of these six cases, however, had had to be rebanded in order to obtain a mean pulmonary to systemic arterial pressure ratio of ≤0·5. In addition, at recatheterisation at least four cases had a mean pulmonary arterial pressure and arteriolar resistance that exceeded or barely fulfilled the Fontan criteria. Given the pronounced increase in pulmonary vascular smooth muscle seen in the infant cases it is perhaps surprising that it may be difficult to band the pulmonary artery satisfactorily on the first occasion. The age at which the pulmonary artery is first banded might be important in this respect. If pulmonary vascular smooth muscle could be shown to regress significantly after birth before showing a secondary increase in response to the high arterial pressure and flow then there might be an optimal age at which the pulmonary artery should be banded. In this series, however, the muscularity was high in four patients with double inlet ventricle without atresia or hypoplasia of either atrioventricular valve (aged 5–8 months) and was similar to that seen in the older patients. This suggests that there is no ideal age at which to band the pulmonary artery, rather it should be banded as soon as possible. The risk of pulmonary artery banding is now low.[4 9] Stefanelli *et al* banded 11 patients with no hospital deaths and a 10 year actuarial survival of 74%.[4] Banded patients with ventriculo-arterial discordance can develop subaortic obstruction,[10] but the only alternative to banding the pulmonary artery appears to be an intracardiac repair in infancy.

The present study demonstrates the difficulty of predicting pulmonary vascular structure and "operability" from the haemodynamic data. Two patients in the present study who had been banded died after a Fontan procedure with a mean pulmonary arterial pressure immediately before operation ≤20 mm Hg. Three patients previously reported died with a preoperative mean pulmonary arterial pressure of 14–25 mm Hg, and at necropsy all three cases showed a significant increase in muscularity.[6] It seems probable that a low pulmonary arterial pressure in these banded patients does not necessarily imply a structurally normal pulmonary vascular bed, and if this is so and muscularity is increased then an intracardiac repair giving a ventricular rather than a atrial dependent pulmonary circulation might be associated with a lower operative morbidity and mortality. When the main chamber is septated, however, the outcome is less satisfactory in patients who do not have pulmonary stenosis.[4 5] It appears that whatever type of intracardiac repair is expected every effort should be made to achieve a structurally normal pulmonary vascular bed beforehand. This may necessitate banding the pulmonary artery on two separate occasions or even ligating the pulmonary artery and performing an aortopulmonary anastomosis.

In patients with double inlet ventricle and left atrioventricular valve hypoplasia pulmonary venous obstruction exacerbates the pulmonary arterial hypertension. In the present series the three oldest patients with left atrioventricular valve hypoplasia showed a pronounced increase in vein wall as well as in arterial wall thickness and venous intimal fibrosis. Early atrial septectomy should help reduce such damage. In a recently published series there were no deaths in the 14 patients undergoing atrial septectomy, and the 10 year actuarial survival was 76%.[4]

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Percutaneous balloon pulmonary valvuloplasty

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SUMMARY Percutaneous pulmonary valvuloplasty was performed in 27 patients with congenital pulmonary valve stenosis. A fall in the transvalve gradient of at least 15 mm Hg occurred in 22 patients. In five there was little change in the severity of the stenosis; in three of these the pulmonary valve was dysplastic. None of the successfully treated patients had a dysplastic valve. The two other failures, early in the series, were probably due to inadequate balloon size. In one patient the procedure was performed twice, with a successful result from the second dilatation with a larger balloon. Follow up studies in a further six patients showed no evidence of restenosis in those who had been successfully treated and no late improvement in the remainder. There were no important complications.

Percutaneous pulmonary valvuloplasty should be the initial treatment for congenital pulmonary valve stenosis, although when the valve is dysplastic the result is less likely to be satisfactory.

Much experience has been gained in the use of percutaneous balloon angioplasty for acquired peripheral vascular disease and also coronary artery disease.[1–3] In addition, the technique has recently been used to treat various congenital lesions including valvar pulmonary stenosis,[4–6] valvar aortic stenosis,[7] coarctation,[8] postoperative recoarctation,[9] and peripheral pulmonary artery stenosis.[10] Here we report our experience with the technique in 27 patients with congenital pulmonary valve stenosis.

Patients and methods

Percutaneous balloon valvuloplasty was attempted in 27 patients with congenital pulmonary valve stenosis aged 6 days to 20 years (mean 5·9 years). One had undergone an open pulmonary valvotomy seven years before the procedure. None of the remainder had previously been treated surgically. All the patients had clinical evidence of moderate to severe pulmonary valve stenosis.

In five patients the procedure was performed under a general anaesthetic; in the remainder premedication with pethidine or morphine was supplemented, if necessary, with intravenous ketamine.

The right femoral vein was entered percutaneously and a sheath inserted. A cannula was inserted into the right femoral artery to monitor continuously the systemic arterial pressure. In one patient access was via a right brachial cutdown and in another via a left fermoral percutaneous puncture. Full diagnostic catheterisation was performed to confirm the diagnosis and exclude any additional malformations. Only patients with a right ventricular systolic pressure greater than 50 mm Hg at rest were considered for valvuloplasty. Right ventricular cineangiography was performed in the anterior-posterior and lateral projections. The diagnosis of pulmonary valve stenosis was confirmed and the size of the pulmonary valve annulus measured. The external diameter of the catheter was used as a reference length to correct for magnification. The position of the pulmonary valve in relation to the spine in the anterior-posterior projection was noted.

A balloon dilatation catheter was selected once the size of the pulmonary valve annulus was known. In patients treated early in the series a catheter with a balloon 1 or 2 mm smaller in diameter than the annulus was chosen; in patients treated later a catheter with a balloon equal to or 1 to 2 mm greater than the annulus was preferred. We used either a Surgimed angioplasty balloon catheter (maximum inflation pres-

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sure approximately 10 atm) or a Meditech balloon dilatation catheter (maximum inflation pressure approximately 3·5 atm).

Optimally, an end-hole catheter was manipulated into the left pulmonary artery, and through it a 0·89 mm (0·035 inch) exchange guide wire was advanced into the left lower lobe pulmonary artery. In three patients the guide wire could be anchored securely only in the right lower lobe pulmonary artery. The catheter was withdrawn, care being taken to maintain the position of the guide wire so that its tip remained well out in the pulmonary artery. The catheter and sheath were removed. A dilator equal to the external diameter of the uninflated balloon catheter was used to dilate the entry site. Once the balloon catheter had been tested and the balloon purged of air the balloon was deflated and inserted over the guide wire. For the smaller balloon sizes a sheath was used.

The balloon catheter was advanced until the estimated position of the pulmonary valve was at the centre of the balloon. The guide wire was left in place during the dilatation procedure. The balloon was then inflated to its maximum pressure with diluted contrast medium. In most cases an indentation at the site of the pulmonary valve was seen as the balloon was inflated. This was abolished as full inflation was achieved (Figure). The balloon was then rapidly deflated. The inflation-deflation cycle took 15 to 25 seconds. Before subsequent dilatations the position of the balloon was slightly adjusted if necessary. Between one and eight dilatations were performed in each case.

Suction was maintained on the balloon catheter as it was withdrawn through the skin at the groin. An end-hole catheter was then reinserted over the guide wire into the left pulmonary artery. The pulmonary artery and right ventricular pressures on withdrawal were recorded.

Clinical follow up took place one to six months after the procedure. Equilibrium gated radionuclide angiography was performed after the procedure in 10 patients. One patient required a repeat valvuloplasty. In six other patients repeat cardiac catheterisations were performed. In two this was because the initial procedure had been unsuccessful and further surgical treatment was indicated. The minimum time between the initial valvuloplasty and follow up catheterisation was two months.

Results

The transvalve gradient fell by at least 15 mm Hg in 22 patients. This was accompanied by a substantial decrease in the right ventricular pressure in 21 patients. In one (case 24) the right ventricular pressure fell by only 10 mm Hg but the pulmonary artery

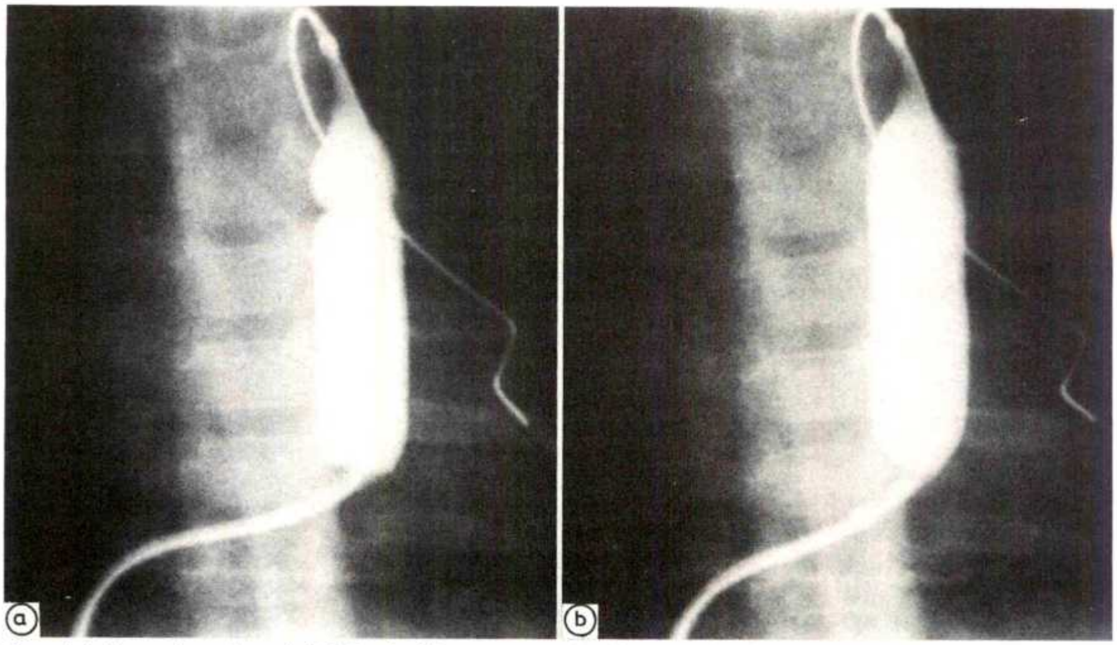

Fig. *A balloon catheter (a) partially inflated while across a stenotic pulmonary valve (the balloon is indented by the valve) and (b) fully inflated, when the indentation disappears.*

pressure rose, producing a fall from 35 to 15 mm Hg in the gradient across the pulmonary valve. In five patients a satisfactory relief of the stenosis was not achieved. Of these five, one (case 9) had both valvar and subvalvar gradients, with a dysplastic valve. Two others (cases 6 and 13) also had dysplastic pulmonary valve leaflets as judged from the right ventricular angiograms. One of these two patients (case 6) had previously undergone an open pulmonary valvotomy. None of the patients in whom the outcome was successful was judged to have a dysplastic valve on the cineangiogram.

One child (case 5) underwent the procedure twice. During the first dilatation, early in the series, a 10 mm Surgimed balloon catheter was used. The measured diameter of the pulmonary valve annulus was 13 mm. The right ventricular pressure fell from 65 mm Hg to 55 mm Hg. Ten months later the right ventricular pressure was found to be 70 mm Hg so repeat valvuloplasty was performed with a 12 mm Meditech balloon catheter. The right ventricular pressure fell to 40 mm Hg. Table 1 shows the haemodynamic results in all patients.

The mean (SD) ratio of systolic right ventricular to femoral artery pressure in all patients before dilatation was 0·81 (0·39) and immediately after valvuloplasty 0·47 (0·17). Comparing these results by a paired t test shows this to be a highly significant fall ($t=5·22$, $p<0·001$). The mean systolic pressure gradient from the right ventricle to the pulmonary artery before dilatation was 64·4 (30·1) mm Hg; after dilatation it fell to 27·0 (12·1) mm Hg. Again a paired t test shows this to be a highly significant fall ($t=5·89$, $p<0·001$).

In most patients the systemic blood pressure fell during the time the balloon was inflated. In one (case 2) there was no fall in the systolic blood pressure, even though a good result was achieved. The blood pressure rose again spontaneously in every case as the balloon was deflated. The longest period of hypotension was 50 seconds (case 12).

In 12 patients bradycardia developed during the balloon dilatation. This also was self limiting. One patient (case 13) developed complete heart block during the first dilatation with a ventricular rate of 40 beats/minute. This reverted spontaneously to normal conduction after 120 seconds. In this case the patient had a dysplastic valve; further dilatations were not attempted.

Two of the older patients who were not fully sedated during the procedure lost conciousness when the balloon was inflated, and one 3 year old patient (case 23) had a convulsion that stopped when the bal-

Table 1 *Haemodynamic data from patients listed in chronological order*

Case No	*Age*	*Systolic pressures (mm Hg)*						*Balloon diameter (mm)*	*Pulmonary valve diameter (mm)*
		Before			*After*				
		RV	*PA*	*FA*	*RV*	*PA*	*FA*		
1	11 years	65	20	125	40	15	110	12	13
2	16 months	75	20	85	40	20	85	7–9	10
3	3 years	60	25	100	45	25	100	9	16
4	3 years	55	18	90	50	15	85	10	12
5 1st	16 months	65	20	90	55	18	90	10	13
2nd	2 years	70	15	90	40	18	105	12	13
6	17 years	80	10	115	60	10	125	20	24
7	12 years	90	30	140	32	25	120	20	19
8	6 days	110	15	85	45	25	80	7	8
9	5 months	70	15	70	60	15	75	7	11
10	20 years	70	20	155	50	20	150	20	22
11	7 years	95	20	120	28	20	130	15	14
12	16 months	70	15	75	35	15	75	15	14
13	1 month	95	15	90	90		90	10	10
14	2 years	125	30	135	45	28	110	12	13
15	11 years	75	25	105	35	15	70	12	12
16	4 years	65	16	110	65	22	145	15	14*
17	13 months	70	16	90	50	18	90	15	14
18	5 years	180	9	75	50	10	85	18	16
19	6 years	125	18	105	55	20	95	15	14
20	12 years	70	12	125	50	12	110	20	20
21	14 years	85	22	150	35	18	135	20	18
22	7 years	60	30	130	35	20	125	15	15
23	3 years	135	15	110	35	15	110	12	13
24	9 months	60	25	125	50	35	115	12	12
25	4 years	90	25	110	50	15	95	12	12
26	10 years	60	17	90	35	20	100	20	19
27	8 years	75	20	125	50	25	140	20	19

*Echocardiographic measurement.
RV, right ventricle; PA, pulmonary artery; FA, femoral artery.

loon was deflated. The convulsion recurred during subsequent dilatations.

No patient showed any neurological sequelae after pulmonary balloon valvuloplasty. Local complications at the puncture site did not develop in any patient. All patients were discharged from hospital within four days except one infant, in whom the procedure had failed, who underwent surgical valvotomy.

On clinical follow up the quality of the murmur was judged to have changed in most of the successful cases. Clinical evidence of pulmonary incompetence was not found in any patient. Analysis of the equilibrium gated radionuclide angiograms showed that the mean (SD) radionuclide ratio of left ventricular to right ventricular stroke counts was 1·2 (0·2). A ratio of less than 0·7 indicates right ventricular volume overload.[11] No patient fell into that category.

Follow up studies showed that in the four patients judged to have a good immediate result the fall in right ventricular pressure was maintained. In two other patients, who had poor immediate results, there was no late fall in right ventricular pressure (Table 2).

Table 2 *Follow up data on six patients*

Case No	*Systolic pressures (mm Hg)*		
	RV	*PA*	*FA*
1	45	22	125
3	45	25	105
6	75	15	125
7	55	35	150
8	40	15	85
9	100	20	70

RV, right ventricle; PA, pulmonary artery; FA, femoral artery.

Discussion

The results presented here together with previous published reports of percutaneous balloon pulmonary valvuloplasty[4–6 12] indicate that it can be an effective short term treatment for most patients with congenital pulmonary valve stenosis, including the newborn.

No major complications of the technique have been reported, and in most cases the right ventricular pressure has fallen sufficiently after the procedure to preclude the need for further treatment. There is no clinical evidence that pulmonary regurgitation is caused by the procedure, and in our patients radionuclide studies did not show evidence of right ventricular volume overload. These results compare favourably with those from open pulmonary valvotomy, where the postoperative right ventricular pressure is often 40 mm Hg or more and pulmonary incompetence often occurs.[13]

It is not certain as yet how the valves subjected to balloon valvuloplasty are torn. In one case treated under direct vision in our unit during surgery the valve was split along a fused commissure, but Lababidi and Wu have reported a case in which a bicupsid valve was torn into the cusp tissue itself.[5]

The physical principles of the dilatation of stenoses with balloons indicate that to apply the maximum dilating force to the stenotic lesion the biggest balloon feasible should be used.[14] This consideration led us to prefer a balloon equal to or slightly larger than the pulmonary valve annulus for the patients treated later in our series. Though we used balloons with both high and low maximum inflation pressures, our data are insufficient to judge whether better results are obtained with the high inflation pressure balloon.

Generally the best results in our series of patients were seen in those with the highest initial right ventricular pressure. In those with lower pressures the results were not so dramatic, and follow up studies will be essential in judging the success of the technique. Of the six patients restudied, the four who had had a good immediate result had maintained the lower right ventricular pressure. There was no late fall in the two others, in whom the initial result was unsatisfactory.

Results were unsatisfactory in five of our patients. In three the valve was dysplastic. Such valves may not be amenable to this form of treatment.[4] Indeed, we have not seen a successful outcome in any patient who appeared to have a dysplastic valve on cineangiography. In one of these three there was, in addition, a subvalvar obstruction, which despite being entirely muscular did not regress after the valvuloplasty. Two of these patients with dysplastic valves subsequently underwent surgery. Although the valve cusps in these patients were found to be thick and immobile, they were not fused. It is therefore not suprising that the balloon dilatation did not improve their function.

In the two other patients in whom treatment was unsatisfactory we believe that the balloon used may have been too small. In one we had for technical reasons to rely on an echocardiographic measurement of the size of the pulmonary valve annulus. In our experience this has been less satisfactory than an angiographic measurement. In the other (case 4), treated early in the series, we used a 10 mm balloon for a measured 12 mm pulmonary valve annulus. We would now consider a balloon of at least 12 mm essential. Similarly, in case 5 the first dilatation with a 10 mm balloon was unsuccessful, while a subsequent dilatation with a 12 mm balloon produced an appreciable fall in right ventricular pressure.

Two of our patients lost consciousness during the procedure, and one had convulsions. To protect patients from a potentially unpleasant experience we recommend that they are all effectively anaesthetised before balloon dilatation is attempted. We have generally used ketamine anaesthesia. We would also recommend that each patient is given oxygen to breathe by face mask and that a prophylactic dose of atropine is administered before the dilatation is begun.

Experience to date indicates that percutaneous balloon valvuloplasty is safe, effective, and can be performed at any age. The limiting factor is judgment of the balloon size to be used. We believe that our recent, more aggressive approach is achieving better results. Although hard and fast indications have not yet been established, it is currently our treatment of choice for congenital pulmonary valve stenosis. When the valve is dysplastic the procedure is not as successful, but at present we would still recommend that balloon valvuloplasty should be the initial choice of treatment.

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Cross sectional echocardiographic diagnosis of total anomalous pulmonary venous connection

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SUMMARY Total anomalous pulmonary venous connection can be diagnosed by cross sectional echocardiography. Information is, however, lacking concerning the diagnostic accuracy of this imaging method and any factors which may influence it. To predict the pulmonary venous connection 463 patients with congenital heart disease who had angiographic confirmation were prospectively examined. Total anomalous pulmonary venous connection was present in 34 (7%) patients and correctly detected in 33 (97% sensitivity). There were two false positive results (99% specificity). All 23 patients with atrial situs solitus with or without associated congenital heart defects were correctly detected. One false negative result occurred in a patient with right atrial isomerism and complex congenital heart disease with decreased pulmonary blood flow.

Diagnosis of the type of total anomalous pulmonary venous connection, including the site and other anatomical details, was analysed and was correct in 24 of 34 (71%) patients. Errors included (*a*) incorrect prediction of the site of total anomalous pulmonary venous connection in five patients with right atrial isomerism, atrioventricular canal defect, and pulmonary atresia, (*b*) details of confluence interconnection in three of four patients with the mixed type of connection, (*c*) undiagnosed pulmonary venous obstruction in three of the patients with right atrial isomerism, and (*d*) failure to predict common pulmonary vein atresia in one patient.

Factors which were related to incorrect echocardiographic diagnosis were abnormal atrial situs, mixed total anomalous pulmonary venous connection, and associated congenital cardiac defects, whereas age, weight, sex, clinical condition, and time during the study were not related.

It is concluded that cross sectional echocardiography can be used to diagnose accurately total anomalous pulmonary venous connection. This method can be the definitive imaging and diagnostic method in symptomatic infants with total anomalous pulmonary venous connection who have atrial situs solitus, unifocal pulmonary venous connection, and no evidence of other major congenital cardiac defect.

Reports from several centres have shown that the diagnosis of total anomalous pulmonary venous connection can be made by cross sectional echocardiography.[1-3] The sensitivity and specificity of this method in detecting total anomalous pulmonary venous connection in children with suspected congenital heart disease are unknown. Also lacking is information concerning the factors which influence the confidence of this diagnosis by cross sectional echocardiography. Once total anomalous pulmonary venous connection is detected, a complete examination should be performed to exclude other associated congenital heart disease and to define the details of pulmonary venous connection. Because cross sectional echocardiography may potentially be the definitive diagnostic method for this abnormality, we prospectively predicted the pulmonary venous connection in 463 patients. The data were analysed to determine (*a*) the predictive accuracy of cross sectional echocardiography in detecting total anomalous pulmonary venous connection and (*b*) the limitations of cross sectional echocar-

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diography in assessing the details of total anomalous pulmonary venous connection in children with congenital heart disease.

Patients and methods

Between July 1982 and August 1983, 463 consecutive patients underwent cross sectional echocardiography in whom the presence of a pulmonary venous connection was unknown. All studies were performed with Advanced Technology Laboratories echocardiographic equipment (MK600 or 300LX) using either 3, 5, or 7·5 MHz transducers and most were performed and interpreted by a doctor. Multiple scanning approaches, including subcostal, parasternal, and suprasternal, were combined in order to visualise all of the pulmonary veins and predict the normal or abnormal connection of each pulmonary vein (Fig. 1).[2] A complete segmental echocardiographic examination was performed as previously described,[4] and the atrial situs was determined using previously published techniques.[5 6] Abnormal atrial situs was confirmed by the angiographic appearance of the atrial appendages or by the radiographic appearance of the bronchi[7] in all patients and by necropsy in four. In this way the location of the morphologically left

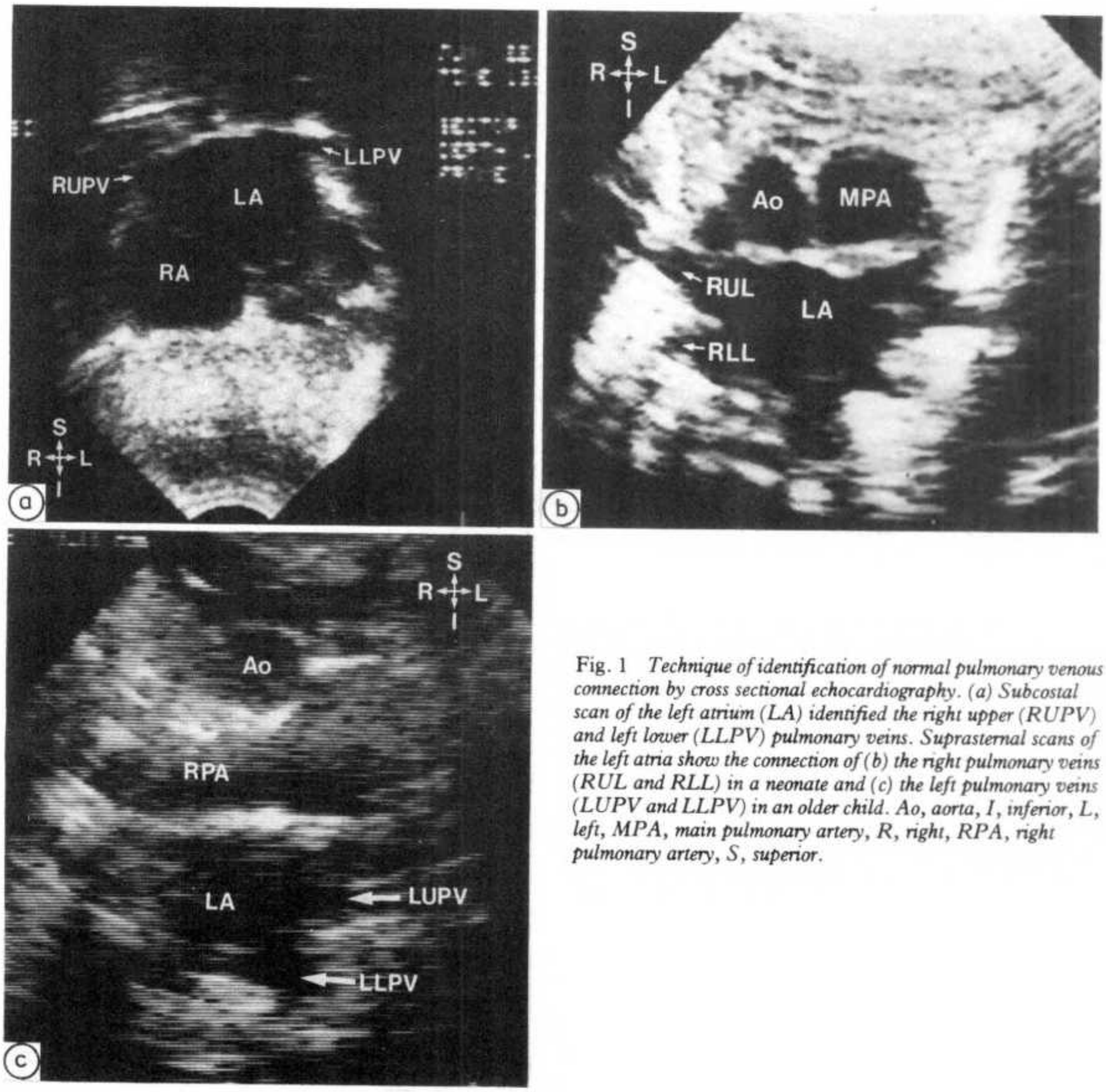

Fig. 1 *Technique of identification of normal pulmonary venous connection by cross sectional echocardiography. (a) Subcostal scan of the left atrium (LA) identified the right upper (RUPV) and left lower (LLPV) pulmonary veins. Suprasternal scans of the left atria show the connection of (b) the right pulmonary veins (RUL and RLL) in a neonate and (c) the left pulmonary veins (LUPV and LLPV) in an older child. Ao, aorta, I, inferior, L, left, MPA, main pulmonary artery, R, right, RPA, right pulmonary artery, S, superior.*

atrium (the expected site of normal pulmonary venous connection) was identified. In atrial situs solitus, normal pulmonary venous connection was defined as connection of all of the pulmonary veins to the left sided morphologically left atrium. Therefore, in situs solitus total anomalous pulmonary venous connection was excluded in the presence of at least one pulmonary vein connecting to the left sided atrium. Patients with partial anomalous pulmonary venous connection have a different presentation, their anomaly is associated with other congenital defects, and their morphological spectrum is different; these patients were included in the group of patients without total anomalous pulmonary venous connection and not analysed further. In patients with bilateral right atrial appendages (right atrial isomerism), in whom there is no morphological left atrium, all patients have total anomalous pulmonary venous connection to a pulmonary vein confluence which then may connect to either atria or to one of the systemic veins. In this situation even confluent connection to the left sided atrium is total anomalous connection and therefore these patients were included. During the study none of the patients with left isomerism had total anomalus pulmonary venous connection. Those with pulmonary venous connection to both atria were classified as having "partial" anomalous pulmonary venous connection.

Table 1 *Details of patients with total anomalous pulmonary venous connection*

Case No	*Sex*	*Age*	*Situs*	*Connection site*	*Associated CHD*	*Cross sectional echocardiographic diagnosis*
1	M	8 yr	RI	RA	CAVO, CA	Correct
2	F	6 mnth	Solitus	LVV	—	Correct
3	M	10 d	Solitus	BD	—	Correct
4	M	5 wk	Solitus	LVV	—	Correct
5	M	7 mnth	Solitus	Mixed (LVV+CS)		Correct
6	M	2 mnth	Solitus	Azygos vein		TAPVC detected; right atrium
7	M	19 mnth	Solitus	Mixed (LVV+CS)		Mixed TAPVC detected; non-conflence of pulmonary veins not detected
8	M	1 d	RI	RSVC (obstructed)	CAVO, CA, PA	TAPVC not detected (false negative); obstruction and site of connection not diagnosed
9	M	1 d	Solitus	Common pulmonary vein atresia		TAPVC detected
10	M	1 d	RI	RA	CAVO, CA, PA	TAPVC detected; site of connection not diagnosed
11	M	2 yr	Solitus	RA	—	Correct
12	F	3 yr	Solitus	LVV	TGA (C)	Correct
13	M	1½ mnth	Solitus	CS	—	Correct
14	F	19 mnth	Solitus	LVV		Correct
15	M	2 mnth	Solitus	CS	PA, VSD	Correct
16	F	1 d	RI	RA	CAVO, PA	TAPVC detected; site of connection not diagnosed
17	F	2 yr	Solitus	Mixed (LVV+CS)	—	Mixed TAPVC detected; non-confluence of pulmonary veins not detected
18	F	5 d	Solitus	BD	—	Correct
19	F	1 d	RI	RSVC	CAVO, DORV, PS	TAPVC detected; site of connection not diagnosed
20	M	1 d	Solitus	CS	—	Correct
21	M	3 wk	Solitus	BD	—	Correct
22	F	12 mnth	Solitus	LVV		Correct
23	M	1 mnth	Solitus	LVV	—	Correct
24	M	7 mnth	Solitus	RA	—	Correct
25	F	3 mnth	Solitus	LVV		Correct
26	M	3 mnth	RI	LSVC (obstructed)	CAVO, DIRV, DORV	TAPVC detected; obstruction and connection not diagnosed
27	M	15 yr	RI	Left side of CA	CAVO, SORV, PA	Correct
28	M	1 mnth	Solitus	Mixed (BD+RSVC)		Mixed detected; predicted connection to RA instead of RSVC
29	M	1 d	RI	LSVC	CAVO, SORV, PA	Correct
30	M	8 yr	Solitus	RSVC	TGA, VSD, PS	Correct
31	M	13 mnth	Solitus	CS	—	Correct
32	M	3 wk	RI	LSVC (obstructed)	CAVO, DIRV, PA	TAPVC detected; obstruction and connection not diagnosed
33	M	4 yr	RI	Left side of CA	CAVO, DIRV, PS	Correct
34	M	1 yr	RI	Left side of CA	CAVO, TGA, PS	Correct

BD, below the diaphragm (obstructed); CA, common atrium; CAVO, common atrioventricular valve orifice; CHD, congenital heart disease; CS, coronary sinus; DIRV, double inlet right ventricle; DORV, double outlet right ventricle; LSVC, left superior vena cava; LVV, left vertical vein; PA, pulmonary atresia; PS, pulmonary stenosis; RA, morphological right atrium; RI, right atrial isomerism; RSVC, right superior vena cava; SORV, single outlet right ventricle; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries (ventriculoarterial discordance); TGA, (c) corrected transposition; VSD, ventricular septal defect.

Table 2 *Detection of total anomalous pulmonary venous connection by cross sectional echocardiography and angiography*

Angiography	*Echocardiography*			
	True		*False*	
	+	−	+	−
True				
+	33			1
−		427	2	

+, positive; −, negative.
Sensitivity 97%, specificity 99%.

The details of pulmonary venous connection by angiography were available in all patients, and the findings by cross sectional echocardiography were compared with the angiographic findings. Echocardiography was performed before any angiographic study in 380 patients and after in 83. All the echocardiographic examinations were performed without knowledge of this information in the latter group in an attempt to preserve the prospective aspect of echocardiographic prediction of pulmonary venous connection. The first cross sectional echocardiographic examination was analysed and the patients were excluded if the examiner was familiar with the diagnosis. Errors in detection of total anomalous pulmonary venous connection were expressed as false positive or false negative results and the sensitivity in detection was expressed as the number of true positive results divided by the sum of the true positive results plus the number of false negative results. Diagnostic errors were further analysed and factors affecting diagnostic accuracy assessed. The group of patients with any diagnostic error was compared with the other patients with total anomalous pulmonary venous connection in whom diagnosis was entirely accurate. Discrete variables such as sex or presence of abnormal situs were compared with χ^2 methods. Linear variables such as weight and age were tested by

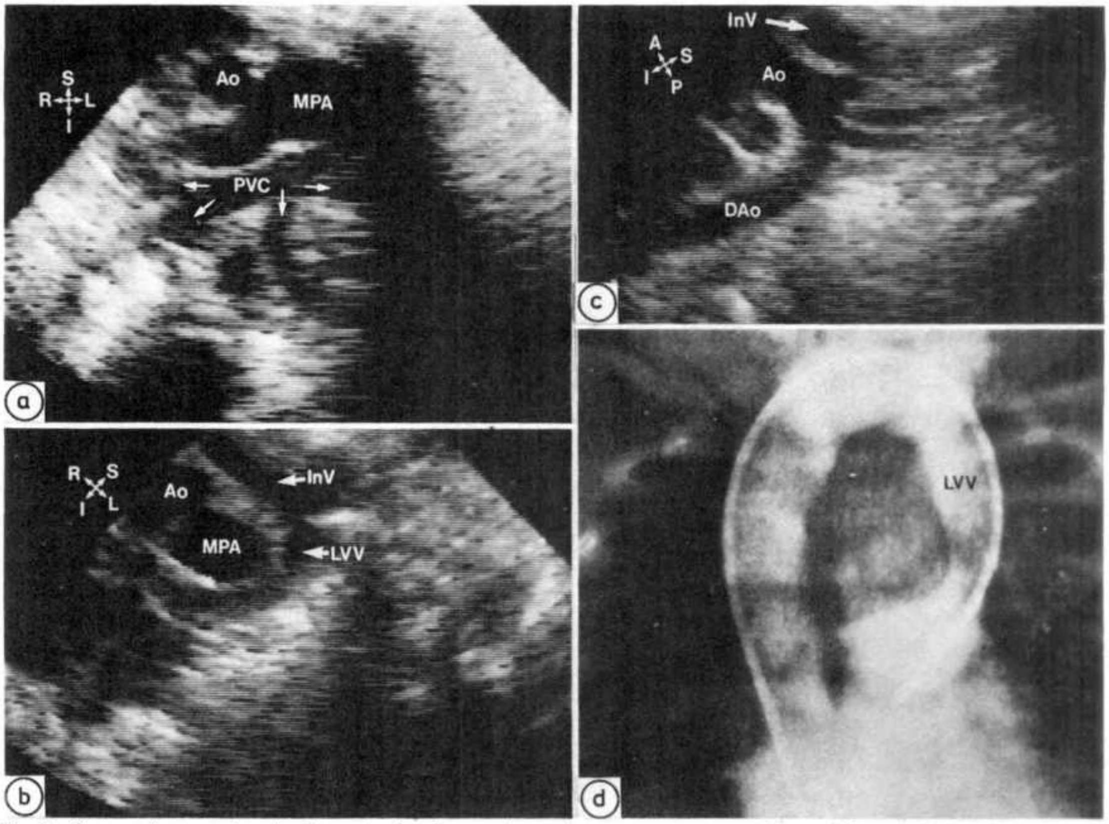

Fig. 2 *Segmental approach to the diagnosis of total anomalous pulmonary venous connection to a left vertical vein. Cross sectional echocardiograms showing (a) the four pulmonary veins (white arrows) connecting to a pulmonary venous confluence (PVC) in a suprasternal scan and (b) and (c) the left vertical vein (LVV) and innominate vein (InV) dilatation during counterclockwise rotation of the transducer; note the dilatation of the main pulmonary artery (MPA) compared with the aorta (Ao). (d) An angiogram is shown for comparison. A, anterior, DAo, descending aorta, P, posterior. Other abbreviations as in Fig. 1.*

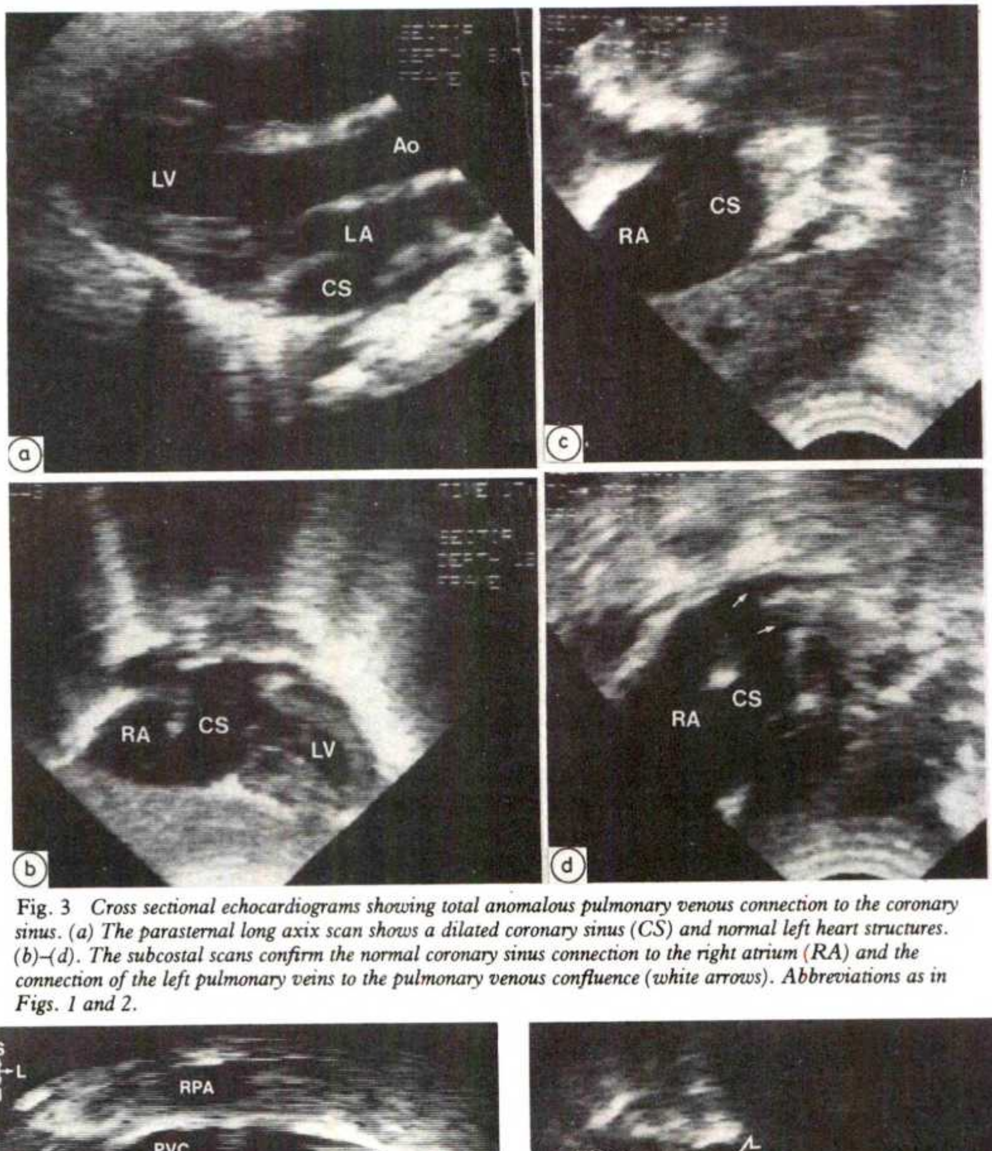

Fig. 3 *Cross sectional echocardiograms showing total anomalous pulmonary venous connection to the coronary sinus. (a) The parasternal long axix scan shows a dilated coronary sinus (CS) and normal left heart structures. (b)–(d). The subcostal scans confirm the normal coronary sinus connection to the right atrium (RA) and the connection of the left pulmonary veins to the pulmonary venous confluence (white arrows). Abbreviations as in Figs. 1 and 2.*

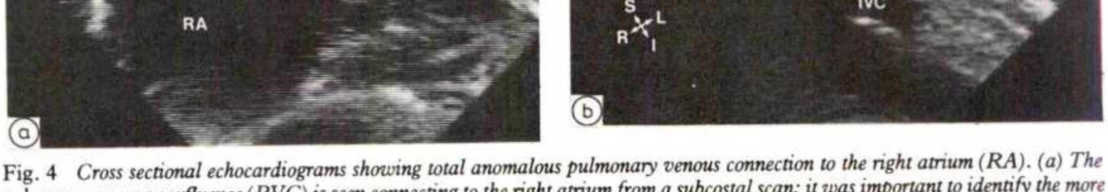

Fig. 4 *Cross sectional echocardiograms showing total anomalous pulmonary venous connection to the right atrium (RA). (a) The pulmonary venous confluence (PVC) is seen connecting to the right atrium from a subcostal scan; it was important to identify the more anterior right pulmonary artery (RPA) to make this diagnosis. (b) The site of pulmonary venous connection is visualised (open arrow) in a saggital plane from a subcostal scan and a large eustachian valve (E) is seen. The superior (SVC) and inferior (IVC) venae cavae are seen connecting to the right atrium. Abbreviations as in Fig. 1.*

comparing the two groups with Student's *t* test. Any variable with a p value <0.05 was considered to be significant. Factors analysed included sex, weight, age, clinical status (ventilator dependent and critically ill scored 1, others 0), type of pulmonary venous connection (supracardiac, cardiac, or infracardiac), atrial situs (normal or abnormal), and presence of other intracardiac congenital defects. Because this study spanned a period of 14 months with the possibility of a learning curve, the first and second seven month periods were compared.

Results

DETECTION OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION

Of the 463 patients, 34 (7%) had total anomalous pulmonary venous connection by angiography (Table 1). The sensitivity of detection of these patients was 97% and the specificity was 99% (two false positive results) (Table 2). In the one patient with total anomalous pulmonary venous connection that was not detected early in the study there was coexisting pulmonary atresia and low pulmonary blood flow with right isomerism and asplenia. False positive diagnoses of total anomalous pulmonary venous connection occurred in two patients: one was a neonate with an atrioventricular canal defect, pulmonary atresia, normally connecting veins, and atrial situs solitus and the other was an older infant with an unusually large atrial defect and a large coronary sinus.

The appearance of the intracardiac anatomy aided in the detection of total anomalous pulmonary venous connection. In situs solitus after the neonatal period, a typical pattern of intracardiac anatomy was found consisting of right heart dilatation and a relatively small left atrium and left ventricle.

TYPE OF TOTAL ANOMALOUS PULMONARY VENOUS CONNECTION (TABLE 1)

The connection of all four pulmonary veins and the subtype of total anomalous pulmonary venous connection plus all other intracardiac and extracardiac anatomy were defined correctly in 24 of 34 (71%) patients. Total anomalous pulmonary venous connection was supracardiac in 14: left vertical vein in seven (Fig. 2), right superior vena cava in three, left superior vena cava in three, azygos vein in one. There was intracardiac connection in 12: coronary sinus in four (Fig. 3), right atrium in five (Fig. 4), and left atrium in three with right isomerism. Infracardiac connection was present in three (below the diaphragm to portal or hepatic veins) and mixed in four (Fig 5). One patient had common pulmonary vein atresia.

There were three factors which related to diagnostic errors: presence of complex congenital heart disease with atrial isomerism (Fig. 6), mixed type of total anomalous pulmonary venous connection, and pulmonary vein atresia. Other factors such as the sites of anomalous pulmonary venous connection did not affect the accuracy of diagnosis. Presence of other congenital cardiac defects and presence of atrial isomerism were covariate owing to the frequent association of atrioventricular canal defect and severe pulmonary stenosis or pulmonary atresia with this situs abnormality. The pulmonary venous connection was diagnosed correctly in three patients with situs solitus and associated intracardiac defects. Pulmonary venous obstruction was present in three neonates with right atrial isomerism and was not diagnosed in spite of the neonatal use of prostaglandin E_1 before palliation of pulmonary atresia or stenosis.

Discussion

Anomalies of pulmonary venous connection are, in themselves, nearly always surgically remediable. They may be isolated or found in association with other types of congenital heart disease. After early reports of the non-invasive diagnosis of total anomalous pulmonary venous connection by M mode echocardiography it was expected that cross sectional echocardiography would be a highly accurate diagnostic technique in this condition.[8-10] Little information is, however, available concerning either the detection of this anomaly or the feasibility of complete anatomical assessment in such patients. Recently, improved echocardiographic equipment and knowledge of tomographic anatomy have allowed the diagnostic accuracy of cross sectional echocardiography in total anomalous pulmonary venous connection to be determined. This study also attempted to define factors which may hinder accurate diagnosis in this condition—namely, *(a)* right atrial isomerism, *(b)* mixed total anomalous pulmonary venous connection (most commonly to the coronary sinus and the left vertical vein), and *(c)* common pulmonary vein atresia. An analysis of diagnostic errors permitted us to construct a profile of the patient with total anomalous pulmonary venous connection who can be detected easily and whose anatomy can be accurately predicted. This information is valuable in assessing the need for surgical treatment of such infants in the newborn period and for diagnostic catheterisation and angiography.

In situs solitus the intracardiac anatomy was uniformly that of a dilated right atrium and ventricle, a relatively small left atrium and ventricle, dilated pulmonary annulus and proximal pulmonary arteries, and a restrictive atrial septal defect. By a combination of suprasternal and subcostal images, all four pulmonary veins were assessed and the mode of anomalous

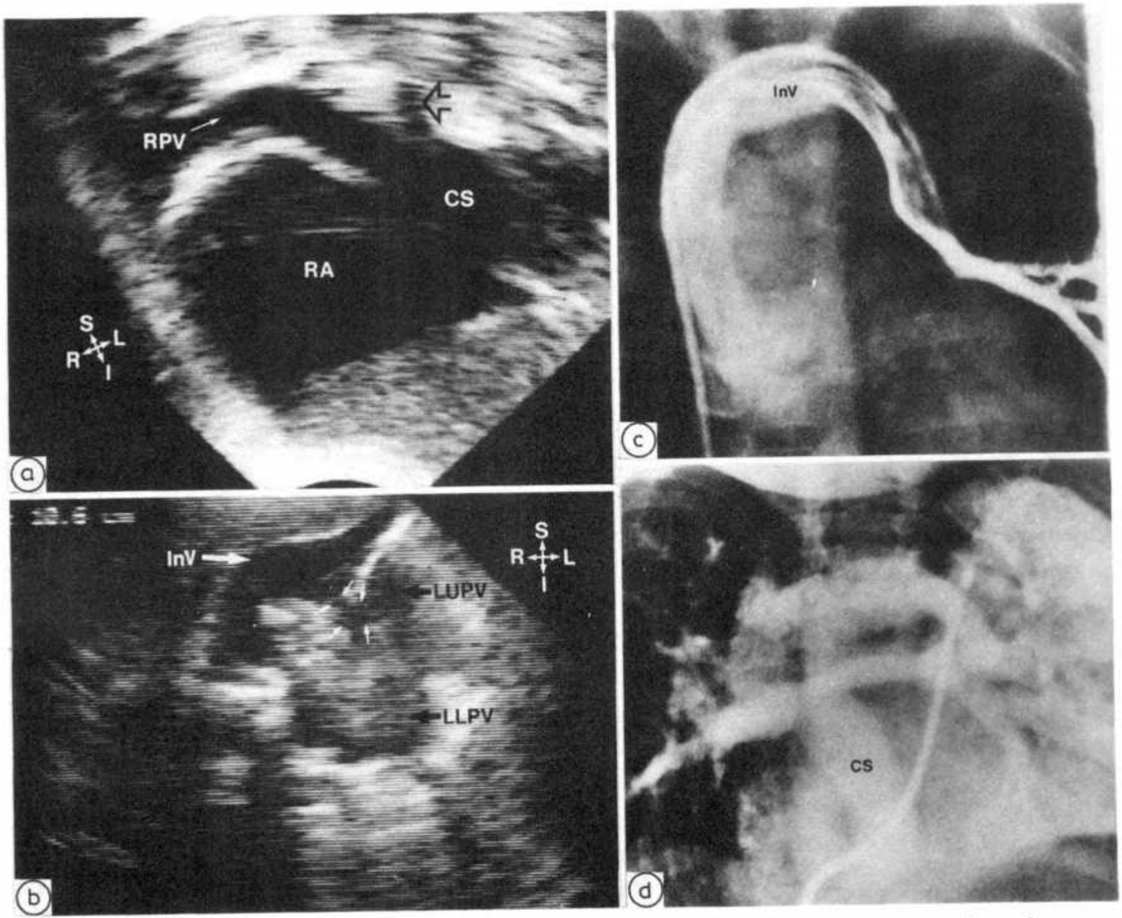

Fig. 5 *Cross sectional echocardiograms ((a) and (b)) showing mixed total anomalous pulmonary venous connection to the coronary sinus (CS) and left vertical vein. (a) The right pulmonary veins (RPV) are identified from subcostal scans connecting to the coronary sinus and then to the right atrium (RA). Evidence of left pulmonary vein connection to the coronary sinus is also present (open black arrow). (b) A suprasternal scan shows the left upper pulmonary venous connection to a short left vertical vein (white arrows) and then the innominate vein (InV). (c) and (d) Angiograms of the same patient illustrate similar difficulty in defining the details of pulmonary venous connection of the mixed type. Injections were performed in the vertical vein (c), and the pulmonary trunk (d) showed left pulmonary venous connection to two sites.*

connection diagnosed. The limitations of cross sectional echocardiography in such patients were related to the sites of connection of the pulmonary venous confluences and interconnections of the pulmonary veins. Abnormalities of each of these factors were recognised by non-invasive assessment alone. False positive diagnosis of total anomalous pulmonary venous connection in situs solitus occurred in one patient with a large atrial septal defect and a left superior vena cava to the coronary sinus and in a neonate with situs solitus and asplenia.

The diagnosis of atrial situs can be made indirectly by cross sectional echocardiography by imaging the position of the inferior vena cava and aorta in relation to the spine at the level of the diaphragm. Specifically, right isomerism is nearly always associated with the aorta and inferior vena cava running together on one or other side of the spine. Because right isomerism has a high association with anomalous pulmonary venous connection and complex congenital heart disease with pulmonary stenosis or atresia, it is important to know the limitations of non-invasive diagnosis in these patients. We found that the site of pulmonary venous connection could not be consistently identified in the presence of low pulmonary blood flow. Furthermore, the frequent association of pulmonary venous obstruction could not be reliably predicted by imaging alone before construction of a systemic to pulmonary

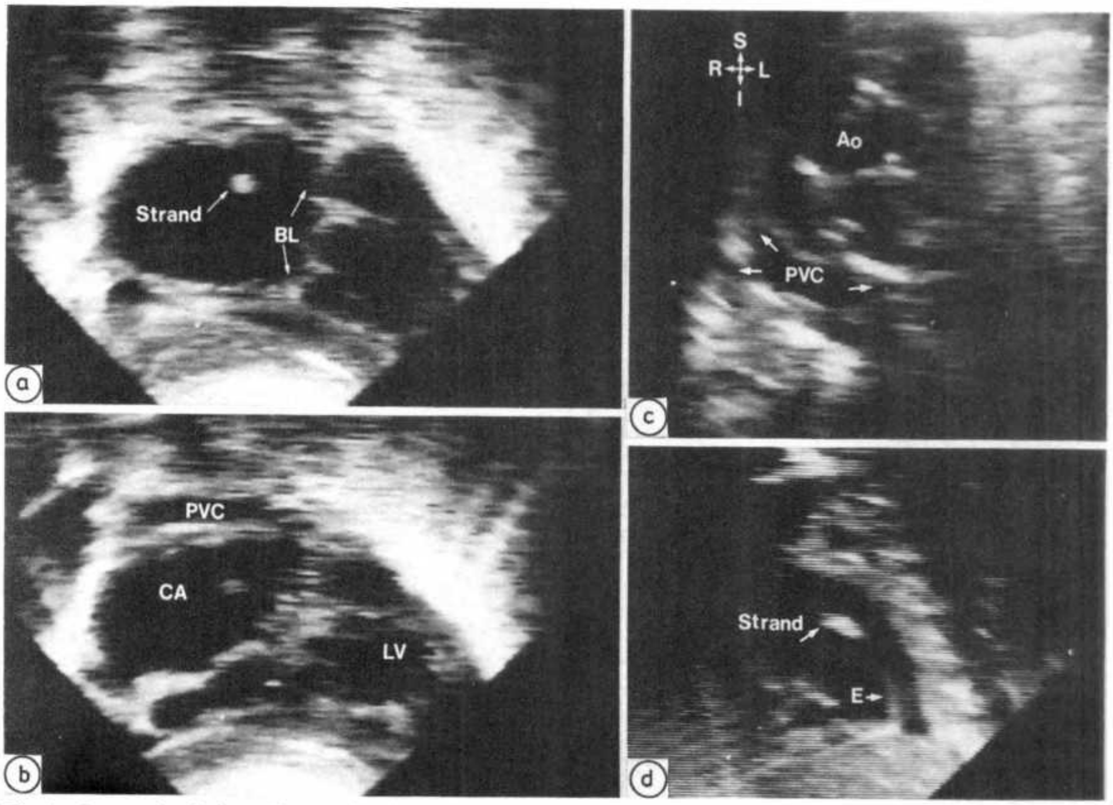

Fig. 6 *Cross sectional echocardiograms showing total anomalous pulmonary venous connection to a posterior confluence (PVC) in an infant with right atrial isomerism. The presence of bilateral right atria is suggested by the presence of an atrial strand (a), the appearance of a common atrium (CA) (b), and a complete atrioventricular canal defect. The location of the confluence and the pulmonary veins connecting to it (white arrows) were defined from suprasternal scans (c). The relation of the atrial strand to the eustachian valve (E) is shown in (d). Note that the site of connection of the confluence is not defined nor is the presence of pulmonary vein obstruction.*

shunt. Almost invariably the failure to identify the site of pulmonary venous connection meant pulmonary venous obstruction. Application of the prostaglandin challenge[11] in the early neonatal period in four such patients failed to show the presence of pulmonary venous obstruction in three who later (3–4 months) died of congestive heart failure after construction of a systemic to pulmonary artery shunt. In the future it is likely that improved knowledge of the dynamics of pulmonary venous flow in total anomalous pulmonary venous connection using Doppler echocardiography[12] will improve detection of this important problem (Fig. 7). In one patient with right atrial isomerism Doppler echocardiography located the pulmonary venous connection to the right superior vena cava, and there was a good correlation between the echocardiographic and angiographic findings retrospectively (Fig. 8).

Mixed total anomalous pulmonary venous connection was present in four patients, all with situs solitus, and there was associated congenital heart disease in one. All were shown to have total anomalous pulmonary venous connection; however, the details of mixed total anomalous pulmonary venous connection were difficult to identify in three patients. Two had pulmonary venous connection to the coronary sinus and the left vertical vein. In this setting, the pulmonary veins may or may not be in continuity, and this anatomical detail will affect the surgical approach. When they are in continuity, the surgical repair consists of using the connection to the coronary sinus and ligating the left vertical vein. When not in continuity, the veins from the left lung to the left vertical vein may be anastomosed to the left atrial appendage[13] or directly to the left atrium. With our current policy at this hospital of using palliation by early balloon atrial septostomy and later blade/balloon atrial septostomy we have avoided early surgical repair of total anomal-

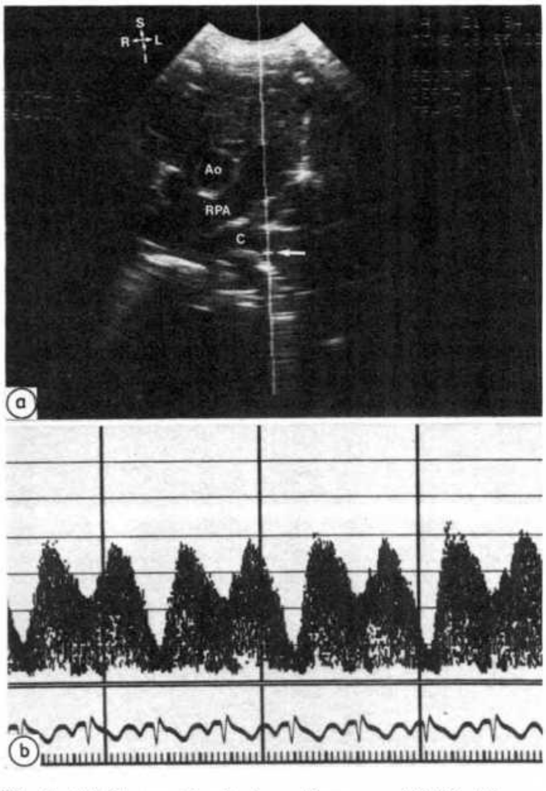

Fig. 7 *(a) Cross sectional echocardiogram and (b) Doppler echocardiogram showing flow velocity in the pulmonary vein confluence (C) in a 2 month old infant with total anomalous pulmonary venous connection to the coronary sinus. Note the low velocity signals (peak of 62 cm/s) at the site of Doppler sampling ((a) white arrow). Abbreviations as in Fig. 1.*

ous pulmonary venous connection in many such patients. This may be important in those in whom a widely patent venous anastomotic channel could be more easily created for the anomalous veins at an older age. The important diagnostic result of this study was the finding that mixed total anomalous pulmonary venous connection could be detected accurately using suprasternal scans.[14]

One patient with common pulmonary vein atresia was found to have anomalous pulmonary venous connection, but the site could not be imaged. At angiography and necropsy the pulmonary veins drained via dilated bronchial veins. This anomaly is extremely difficult to diagnose,[15] and such patients require angiographic study for a definitive diagnosis.

We conclude that cross sectional echocardiography can be used to diagnose accurately total anomalous pulmonary venous connection. This method can be the definitive imaging and diagnostic method in symptomatic infants with total anomalous pulmonary venous connection who have atrial situs solitus, unifocal pulmonary venous connection, and no evidence of other major congenital cardiac defect.

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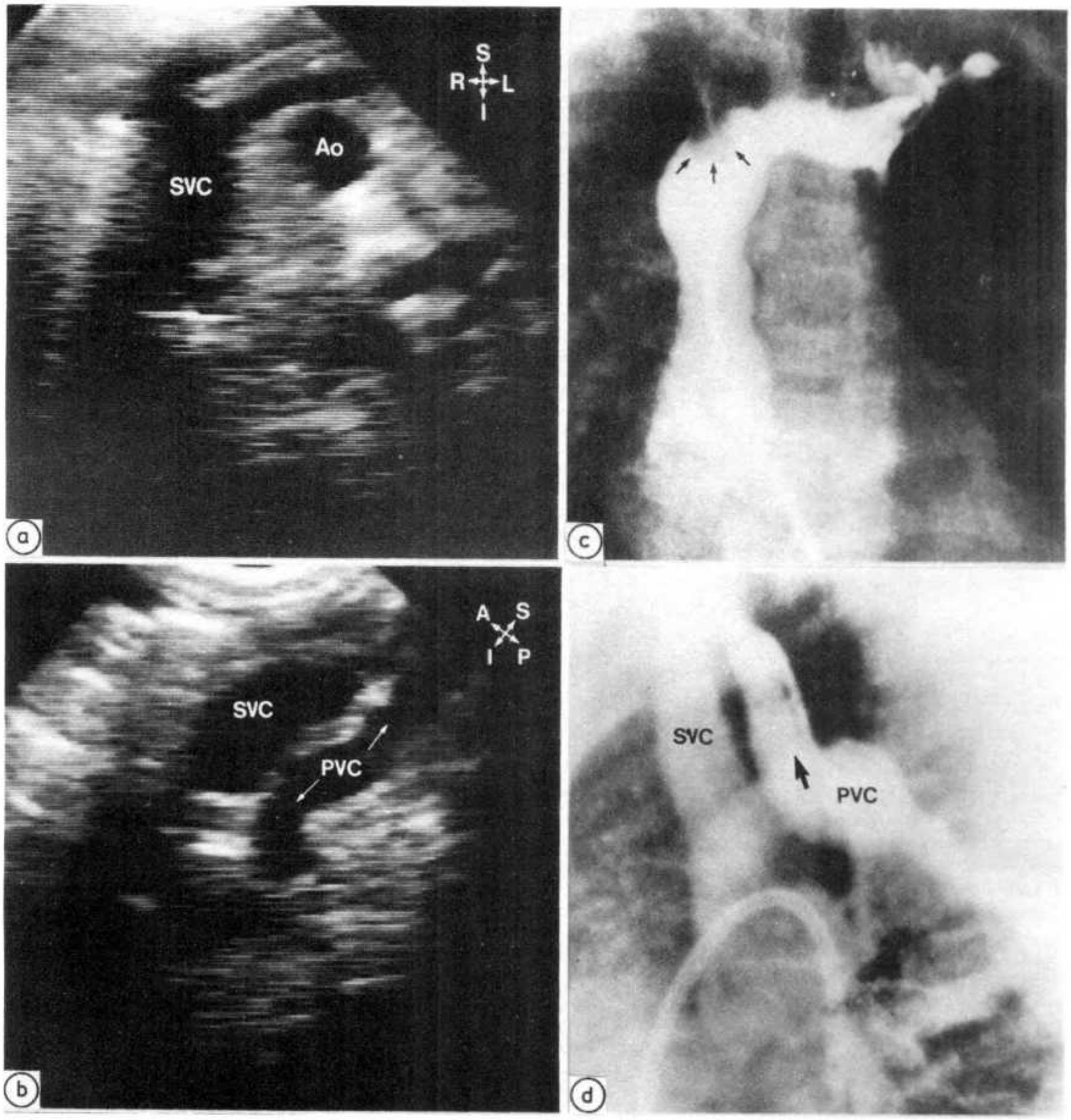

Fig. 8 *((a) and (b)) Cross sectional echocardiograms and ((c) and (d)) angiograms showing complex pulmonary venous connection to the right upper superior vena cava (SVC). (a) In suprasternal scans this structure was dilated, suggesting that this was the site of confluence connection and the angiogram (c) confirmed this; note washout of SVC (black arrows). (b) A saggital parasternal scan and corresponding angiogram (d) show the unusual course of the pulmonary venous confluence. Abbreviations as in Figs. 1 and 2.*

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Superiority of radionuclide over oximetric measurement of left to right shunts

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SUMMARY In 100 children with suspected left to right shunts the ratio of pulmonary to systemic flow was measured both by oximetry and first pass radionuclide angiography. The pulmonary time activity curve from the radionuclide study was analysed by the method of gamma variate fits. There was strong correlation between the two techniques; weaker correlation was found when the shunt was at atrial rather than ventricular level. This difference can be explained only by problems with the oximetric rather than the radionuclide technique. Although there are important limitations to the radionuclide method, it is the more precise and less invasive of the two and is to be preferred when the accurate measurement of left to right shunts is required.

The accurate measurement of left to right shunts is essential in the management of many patients with congenital heart anomalies. In clinical practice this is usually performed oximetrically during cardiac catheterisation. The oximetric method is known to have major drawbacks, which can lead to substantial errors.[1] These problems are worst with shunts at atrial level, when a truly representative mixed venous blood sample is impossible to obtain.

Although other techniques, based on the indicator dilution principle, are available, they are not widely used. Estimation of the ratio of pulmonary to systemic flow by first pass radionuclide angiography is one such method.[2]

Previous studies[3–5] have shown strong correlation between results from the radionuclide technique and oximetry but they have not correlated the two methods separately for different cardiac malformations. We use radionuclide angiography routinely in children with a variety of congenital heart malformations including those with left to right shunts at both atrial and ventricular level. Here we present results from 100 patients who underwent both first pass radionuclide angiography and cardiac catheterisation.

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Patients and methods

We studied 100 children with suspected simple left to right shunts. They were aged 1 week to 19 years (mean 4·51 years). In 81 the radionuclide study and cardiac catheterisation were performed within 24 hours of each other. The greatest time between the two procedures was four months. Patients with a ratio of pulmonary to systemic flow greater than four to one, estimated by either method, were not included in the series. Neither technique is likely to be accurate above this level. The Table lists the diagnosis in each case patient.

RADIONUCLIDE TECHNIQUE

A first pass radionuclide angiogram was obtained in the anterior projection over 20 seconds. Data were collected on a magnetic disk in either list mode or at 32 frames per second and then reframed at two frames per second for analysis. A compact, rapid, bolus of autologous red blood cells labelled with technetium-99m was injected via a cannula in a peripheral vein or a catheter lying in the inferior vena cava. Care was taken to ensure a good quality bolus of the radionuclide, which was flushed in with a large volume of saline (20 ml in an adult, 5–10 ml in an infant). The right antecubital fossa was the preferred site for peripheral injection. Sedation was used if necessary in the younger patients. The dose of radionuclide was 430 MBq (11·6 mCi)/m^2.

Table *Results with two techniques for measuring left to right shunts in 100 patients*

Age	*Diagnosis*	*Ratio of pulmonary to systemic flow*		*Age*	*Diagnosis*	*Ratio of pulmonary to systemic flow*	
		Oximetric	*Radionuclide*			*Oximetric*	*Radionuclide*
1 week	MS+ASD	1·2	1·9	2 years	VSD	1·3	1·2
3 weeks	VSD	2·5	2·4	2 years	VSD	2·5	2·4
4 weeks	VSD	2·1	2·5	2 years	VSD	1·0	1·4
4 weeks	AVSD	3·7	4·0	2 years	VSD	1·6	1·9
6 weeks	VSD	3·0	3·1	2 years	AS	1·0	1·0
3 months	VSD	2·2	2·3	2 years	ASD	1·5	1·5
3 months	VSD	2·0	2·3	2 years	AVSD	3·8	3·0
3 months	VSD	2·1	2·7	2 years	VSD	1·1	1·9
3 months	AS	1·0	1·0	2 years	VSD	2·8	2·3
3 months	VSD	2·2	1·8	2 years	ASD	1·7	2·5
3 months	MS+ASD	1·0	1·5	3 years	ASD	2·0	1·5
5 months	VSD	3·0	2·2	3 years	VSD	1·2	1·3
5 months	VSD	2·2	2·1	3 years	ASD	1·5	2·1
5 months	VSD	2·6	2·4	3 years	ASD	2·0	2·0
6 months	VSD	2·7	2·4	3 years	ASD	1·7	2·1
6 months	VSD	1·8	1·8	3 years	ASD	2·2	2·0
6 months	VSD	2·9	2·8	4 years	VSD	1·6	1·6
6 months	ASD	1·6	2·4	4 years	VSD	1·7	2·1
7 months	AVSD	2·5	1·4	4 years	VSD	1·6	1·5
7 months	ASD	1·8	1·8	4 years	VSD	1·3	1·3
8 months	VSD	2·2	1·9	5 years	ASD	1·0	1·9
9 months	VSD	2·4	2·5	5 years	AI	1·0	1·0
9 months	VSD	1·6	1·4	6 years	C	1·0	1·4
9 months	ASD	2·6	2·6	6 years	AS	1·0	1·0
9 months	ASD+VSD	2·3	2·2	6 years	AS	1·0	1·0
9 months	VSD	1·6	2·1	6 years	ASD	1·7	2·0
10 months	VSD	1·0	1·3	6 years	ASD	2·5	2·2
11 months	VSD	1·1	1·3	8 years	AS	1·0	1·0
11 months	VSD	3·0	2·9	8 years	VSD	1·1	1·8
12 months	VSD	3·4	2·9	8 years	ASD	3·0	2·3
12 months	PAPVD	1·9	2·2	9 years	VSD	1·3	1·6
14 months	VSD	2·9	3·3	9 years	ASD	2·0	1·4
15 months	Normal	1·0	1·2	9 years	BPS	1·0	1·0
15 months	VSD	2·6	2·5	10 years	VSD	2·2	2·3
16 months	VSD	2·0	2·1	10 years	VSD	3·5	3·5
16 months	VSD	2·8	3·2	10 years	ASD	1·1	1·5
16 months	VSD	1·8	2·4	10 years	ASD	1·9	1·7
16 months	VSD	1·5	1·8	11 years	VSD	1·4	1·7
16 months	VSD	2·1	2·0	11 years	AS	1·0	1·0
16 months	ASD	2·2	3·3	11 years	ASD	2·3	3·0
17 months	VSD	2·7	2·3	12 years	ASD	2·4	2·2
18 months	VSD	1·5	1·5	12 years	PS	1·0	1·0
19 months	ASD	3·4	3·0	13 years	VSD	2·2	2·2
20 months	ASD	1·4	1·7	14 years	PS	1·0	1·0
21 months	VSD	2·1	2·2	16 years	AS	1·0	1·0
21 months	AVSD	2·5	4·0	16 years	PS	1·0	1·0
22 months	VSD	1·2	1·6	18 years	AVSD	1·5	1·3
23 months	AVSD	1·8	1·9	18 years	VSD	2·0	1·8
2 years	PS	1·0	1·0	18 years	VSD	1·8	1·7
2 years	C	1·0	1·0	19 years	VSD	1·8	2·1

MS, mitral stenosis; ASD, atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; PAPVD, partial anomalous pulmonary venous drainage; PS, pulmonary stenosis; AS, aortic stenosis; AI, aortic incompetence; C, coarctation; BPS, branch pulmonary stenosis.

OXIMETRIC TECHNIQUE

During investigative cardiac catheterisation performed under sedation blood samples were taken from the superior vena cava, the inferior vena cava, the main pulmonary artery, and a systemic artery. They were taken in rapid sequence when the patient was judged to be in a stable physiological state. The percentage oxygen saturation in each sample was measured spectrophotometrically with a reflectance oximeter.[6 7]

DATA PROCESSING

A background corrected, superior vena cava, time activity curve was used to assess the adequacy of the bolus in the radionuclide study. Of those patients eligible for inclusion in the study, six were rejected because the bolus was split. In those in whom the bolus was judged to be of good quality the time activity curve from a region of interest drawn over the right lung was analysed by the method of gamma variate fits.[3-5] If the bolus was wider than roughly two

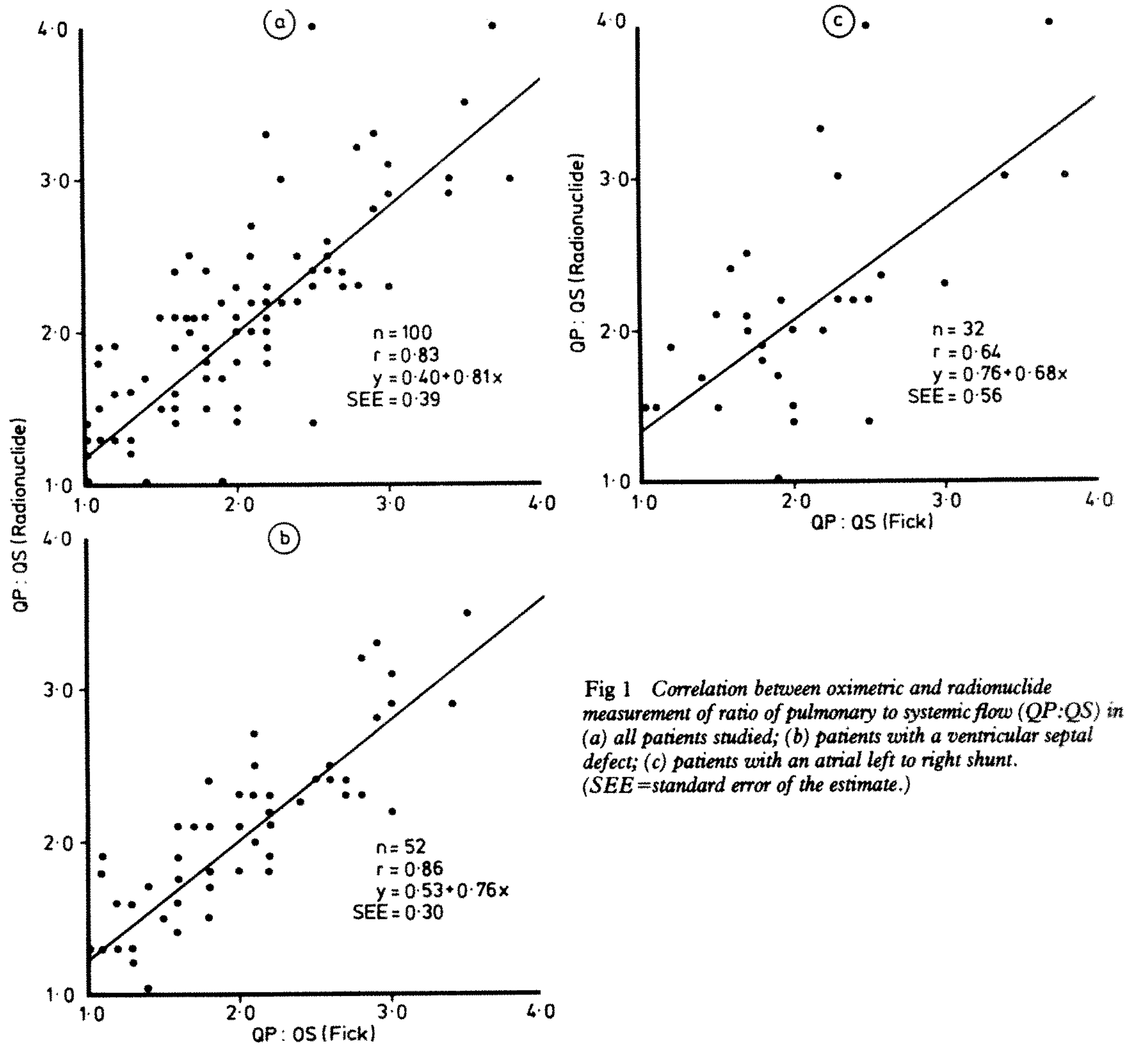

Fig 1 *Correlation between oximetric and radionuclide measurement of ratio of pulmonary to systemic flow (QP:QS) in (a) all patients studied; (b) patients with a ventricular septal defect; (c) patients with an atrial left to right shunt. (SEE = standard error of the estimate.)*

seconds deconvolution analysis was used to correct the pulmonary time activity curve before the shunt analysis was performed.[8 9]

The pulmonary to systemic flow was calculated from the oximetric data by a formula derived from the Fick principle:

$$\frac{Q_p}{Q_s} = \frac{\text{systemic arterial } So_2 - \text{mixed venous } So_2}{\text{pulmonary venous } So_2 - \text{pulmonary arterial } So_2}$$

(So_2 being oxygen saturation). The mixed venous oxygen saturation was estimated from those in the superior and inferior vena cava (SVC and IVC) by the formula:

$$\text{Mixed venous } So_2 = \frac{3 \times \text{SVC } So_2 + \text{IVC } So_2}{4}$$

This formula has been shown to give the most reliable estimate of the true mixed venous oxygen saturation under similar circumstances.[1]

STATISTICAL ANALYSIS

The pulmonary to systemic flow ratios measured by the two techniques were compared by linear regression analysis. The population variances of separate correlations were tested for identity by the F relation. The null hypothesis was rejected when $p<0{\cdot}05$.

Results

The table shows the results for all the patients. Although the correlation for all 100 patients was strong, the correlation coefficient (r) 0·83, and the regression coefficient 0·81, Fig. 1a (scattergram) shows that some points were widely scattered around the regression line. Included in the 100 patients were 16 with no shunt measurable by either technique. The data were then analysed separately for two groups. The first consisted of all patients (52) with a ventricular septal defect and the second of all those with a left to right shunt at atrial level. Patients in the second group included those with atrial septal defects or atrioventricular septal defects and one patient with partial anomalous pulmonary venous connection: 32 patients in all.

The correlation for patients with a ventricular septal defect was strong ($r=0{\cdot}86$). The scatter of points was much less than the overall correlation (Fig. 1b). The correlation for shunts at atrial level was weaker ($r=0{\cdot}64$), and this group (group 2) contained all the most widely scattered points (Fig. 1c). Although the regression equations for the two groups were similar, there was a significant difference between the population variances ($F=3{\cdot}44$, $p<0{\cdot}001$).

Discussion

Our results confirm the validity of the measurement of the ratio of pulmonary to systemic flow by first pass radionuclide angiography in patients with a simple left to right shunt. The correlation remained strong in ventricular shunts even when those patients with no shunt and those with shunts greater than four to one were not included. The strength of the correlation was not therefore dependent on the two ends of the regression relation being fixed.[3 5] Previous studies have shown a wide scatter between the radionuclide and oximetric methods in atrial septal defects,[10 11] but the contrast with the much narrower confidence limits in ventricular septal defects has not previously been shown.

The poorer correlation between the oximetric and radionuclide measurements and the greater population variance when the shunt was at atrial rather than ventricular level cannot be explained by a failing in the radionuclide technique: no additional assumptions are made when the shunt is at atrial level and the acquisition and analysis are identical to that with ventricular shunts. There are problems, however, with the oximetric technique when there is shunting at atrial level. The mixed venous oxygen saturation cannot be measured directly in the presence of a left to right shunt; it has to be estimated from the saturations in the superior and inferior vena cava. The result is inevitably an approximation. The formula we used for this has been shown to give the most reliable estimate of the pulmonary arterial oxygen saturation in patients with no shunt.[1] When there is an atrial shunt the sites of venous sampling are not separated by the tricuspid valve from the inflow of oxygenated blood. The estimation of the true mixed venous oxygen saturation may under these circumstances be impossible.

Other problems exist with the oximetric technique, whatever the level of the shunt. Notably, in applying the Fick principle the patient is assumed to be in a stable physiological state throughout the time of sampling. There is an appreciable spontaneous variation in the cardiac output at rest in man,[12] which is likely to introduce considerable inaccuracies, especially if there is any delay between the taking of blood samples at various sites. There are also inaccuracies in the spectrophotometric measurement of the oxygen saturation of blood; it is recognised to be especially inaccurate above 95% saturation.[6 7] These problems have been well discussed elsewhere.[1]

In view of these considerations we believe that first pass radionuclide angiography offers the more accurate of the two measurements of the ratio of pulmonary to systemic flow in patients with simple left to right shunts.

Nevertheless, the radionuclide technique has some important limitations. Previous authors have rightly emphasised the importance of ensuring a good quality bolus in every study.[3 5] We used an injection technique similar to that of Askenazi *et al.*[3] We, however, preferred the antecubital fossa as the site for venous cannulation and used sedation routinely in the youngest children to ensure that they were calm and in a stable condition during the study. The data must be processed by an experienced operator. As with all curve fitting techniques, unreliable results can easily be obtained by the inexperienced. With meticulous attention to the performance of the study and its analysis, we found that in virtually every case a valid measurement of the pulmonary to systemic flow could be obtained.

There are also some important considerations that make the radionuclide technique invalid in a minority of patients. The left to right shunt is measured as a proportion of the total pulmonary flow, and from this, assuming there is no appreciable right to left shunt, the pulmonary to systemic flow can be calculated. Findings are therefore invalid when shunting is occurring in two directions. A true measure of the pulmonary to systemic flow ratio can be obtained only when there is a pure left to right shunt or when right to left shunting is negligible, as in atrial septal defects.

In patients with no shunt curves can often be fitted that generate a measurement of the pulmonary to systemic flow ratio of 1·2 to 1, or less. This has been noted before, and it has been suggested that it is at least partly due to bronchial arterial and chest wall blood flow.[3] It is probably mostly due to the limitations of the curve fitting method and the statistical

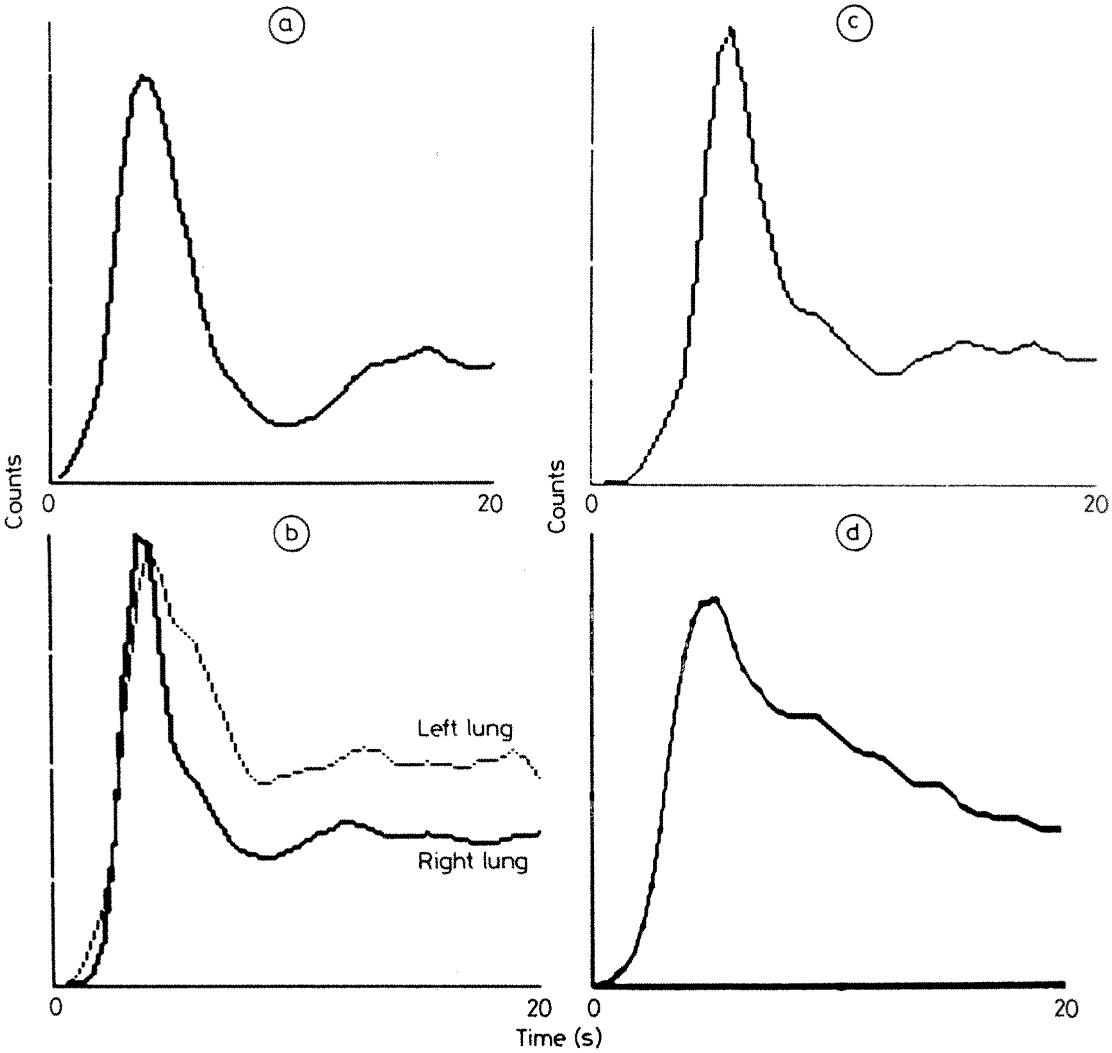

Fig 2 *Time activity curves. (a) A normal curve from a right lung region of interest; the patient had mild pulmonary incompetence. (b) Curves from right and left lungs in a patient with a persistent ductus arteriosus. (c) Curve from right lung of a patient with coarctation of the aorta but no shunt. (d) Curve from right lung in a patient with severe postoperative mitral incompetence. Oximetrically the ratio of pulmonary to systemic flow was 1·3:1; analysis of this curve suggested, incorrectly, that it was much greater.*

noise present in the data. When the pulmonary time activity curve is unequivocally normal (Fig 2a) we do not attempt curve fitting. Using this policy we have never missed an important left to right shunt. Indeed, as previously reported[5 13] the radionuclide technique is more sensitive than oximetry at picking up very small left to right shunts.

With the radionuclide technique, as with oximetry, the overall pulmonary to systemic flow ratio cannot be measured when the lungs are not totally perfused from one central source. This is seen most commonly with a persistent ductus arteriosus but is also applicable when part of the lung is supplied by a major aortopulmonary collateral artery or when there is a patent surgical systemic pulmonary shunt. With a persistent ductus arteriosus the shunt measured from the left lung is often greater than that measured from the right, as Fig 2b shows.[3 13] Neither is a valid measurement of the overall pulmonary to systemic flow ratio, and it is not valid to take a mean of the two measurements. Despite this, previous authors have included such patients in correlative studies between the two techniques.[3-5 10 13]

Patients with coarctation of the aorta may have collateral arteries from the proximal to the distal aorta that cross the lung fields producing a time activity curve that gives the false impression of a left to right shunt, as in Fig 2c.[2] We have noted this even in young infants. It is therefore possible mistakenly to diagnose a left to right shunt or overestimate the magnitude of one when coarctation of the aorta is present.

When cardiac function is very poor or there is severe valvular regurgitation the pulmonary transit time is prolonged, and this may lead to overestimation of the size of the shunt by the radionuclide technique.[2 4 5] Fig 2d illustrates such a case. Under similar circumstances results must be interpreted with extreme caution.

Despite these limitations of the technique the results presented here show its superiority over oximetric measurement in patients with atrial shunts. First pass radionuclide angiography can be performed in outpatients and in critically ill patients at their bedside. The study causes no haemodynamic disturbance and is minimally invasive. It is valid in all age groups. In practice it is probably the most accurate available estimate of the ratio of pulmonary to systemic flow for patients with a simple left to right shunt at any level. Radionuclide angiography should be used to estimate the ratio of pulmonary to systemic flow whenever its accurate measurement is clinically required.

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Pacing in children

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SUMMARY Fourteen children had a permanent pacemaker implanted between May 1967 and July 1983. Postoperative complete heart block was the indication in nine cases, congenital complete heart block in three, and sick sinus syndrome in two. Two patients died, one suddenly and one after aortic valve replacement. A total of 48 pulse generators were implanted; five patients were given an isotopic pacemaker. Twelve patients had epicardial leads implanted initially, and two received a transvenous endocardial system. The lead system implanted initially remained without malfunction in only seven patients. In the other seven patients 20 lead malfunctions occurred. Psychological maturity and physical development seemed to be normal in all 14 children. Improvement in equipment and technique will improve the outlook for paced children in the future.

Paediatric patients form only a minority of the population in a pacemaker clinic. Nevertheless, they account for a substantial proportion of the complications. Postoperative heart block is the most common indication for permanent pacing in children.[1-3] Congenital or idiopathic complete heart block are the other important indications. In children the sick sinus syndrome is now also recognised as an arrhythmia with a potentially fatal outcome.[4-6] The improved reliability and long life of present day cardiac pulse generators justify pacing in symptomatic patients and in those with potentially life threatening conditions.

Patients and methods

From May 1967 to July 1983 a permanent cardiac pacemaker was implanted in 14 children (seven girls and seven boys). They were aged between 27 and 152 (mean age 79, SD 35) months. Their most important clinical features are given in Table 1.

Nine patients developed complete heart block after surgical repair of a congenital heart defect. Three children had congenital complete heart block, one of whom had a ventricular septal defect and valvar pulmonary stenosis. Two children (cases 1 and 2) had sick sinus syndrome without structural heart disease and have been reported elsewhere.[6] Two patients also had severe ventricular arrhythmias (cases 2 and 13).

Adams-Stokes attacks before pacemaker implantation or at the time of pacing malfunction occurred in eight patients (cases 2, 5, 6–9, 11, and 14), whereas no symptoms were related to conduction disturbance in six (cases 1, 3, 4, 10, 12, and 13). One patient (case 1) had sinoatrial disease, and bradycardia had been noticed before birth. This child received a pacemaker because of extreme bradycardia and long ventricular pauses. During the night the ventricular rate varied between 15 and 45 beats/minute. One pause of 4·8, one of 4·6, and numerous pauses of >3 s were recorded. One child (case 3) had asymptomatic congenital complete heart block. Since birth there had been an escape rhythm with narrow QRS. Ambulatory monitoring showed episodes of ventricular asystole lasting up to 4 s and ventricular rates up to 20 beats/min. The second child (case 4) with asymptomatic congenital complete heart block had a nodal (narrow QRS) rhythm slowing down to below 30 beats/min with ventricular pauses lasting up to 5·16 s. Three patients (cases 10, 12, and 13) had postoperative complete heart block. One (case 10) initially received cortisone treatment for atrioventricular block, but this treatment had no effect. A permanent pacemaker was implanted 30 days after surgical repair of his congenital heart defect. In the second patient (case 12) a permanent pacemaker was implanted 35 days after the first surgical intervention. In the third patient (case 13) there was a delay of 21 days between the first operation and pacemaker implantation.

All patients were given ventricular demand or ven-

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Table 1 *Clinical features of 14 paced paediatric patients*

Case No	*Sex*	*Age (yr)**	*Associated heart disease*	*Indication for pacing*	*Duration† of follow up (mnth)‡*	*Total No of pulse generators*	*Present pacemaker type*
1	F	4	—	SS	70	3	Coratomic C101
2	M	5	—	SS	82	2	Medtronic 5985
3	F	7	—	CHB (congenital)	23	1	Medtronic 5985
4	F	12	—	CHB (congenital)	13	1	Coratomic C101
5	F	4	VSD, PS(V)	CHB (congenital)	73	1	Cordis 190A
6	F	2	VSD, PDA	CHB (postoperative)	148	8	Coratomic C101
7	M	7	VSD, PS(I)§	CHB (postoperative)	207	8	Coratomic C101
8	M	4	VSD, PS(I)	CHB (postoperative)	87	2	CPI 523
9	F	6	VSD	CHB (postoperative)	160	4	CPI 505
10	M	7	ASD‖	CHB (postoperative)	135	3	CPI 504
11	F	5	AC, SAS	CHB (postoperative)	47	1	CPI 505
12	M	4	VSD, PS(I)	CHB (postoperative)	177	6	Coratomic C101
13	M	11	TF	CHB (postoperative)	54 (sudden death)	3	
14	M	8	SAS	CHB (postoperative)	84 (postoperative death after AVR)	5	

*At the time of pacemaker implantation.
†Until 31 August, 1984.
‡After first pacemaker implantation.
§Absence of pulmonary valve.
‖Ostium primum type with cleft mitral and cleft tricuspid valve.
AC, aortic coarctation; ASD, atrial septal defect; AVR, aortic valve replacement; CHB, complete heart block; PDA, persistent ductus arteriosus; PS(I), infundibular pulmonary stenosis; PS(V), valvar pulmonary stenosis; SAS, subvalvar aortic stenosis; SS, sick sinus syndrome; TF, tetralogy of Fallot; VSD, ventricular septal defect.

tricular fixed rate pacemakers. Gradually, we had started to prefer atomic pacemaker implantation in children, and so five patients had the small size Coratomic C101 atomic pacemaker. Paediatric suturable epicardial electrodes (Cordis 323–543 and Medtronic 5815A) were preferred. Only two patients received a General Electric bipolar epicardial pacing system as the initial implant. A transvenous endocardial pacemaker system was used as the initial implant in only two children. In 13 patients initial implantations and generator replacements were performed under general anaesthesia. In only one patient (case 4) was a transvenous pacing system implanted under local anaesthesia.

During the follow up of these patients, special attention was given to the presence or absence of escape rhythms occurring after inhibition of the ventricular demand pacemaker by chest wall stimulation. The technique of chest wall stimulation and its application in the pacemaker clinic has been reported elsewhere.[7]

Results

Follow up after implantation of a permanent pacemaker varied between 13 and 207 (mean 97·1, SD 59) months. Two patients died. Sudden death occurred in one boy (case 13), who was known to have severe ventricular arrhythmias, and one (case 14) died postoperatively after aortic valve replacement seven years after his first operation for subvalvar aortic stenosis. One patient (case 2), who was known to have asymptomatic sinus bradycardia and sinuatrial block, collapsed while playing at school. He was given mouth to mouth respiration and arrived at the emergency department within 10 minutes. Repeated episodes of ventricular tachycardia alternated with periods of atrial and ventricular standstill. After the implantation of a permanent pacemaker he recovered completely.

In the 14 children we implanted a total of 48 pulse generators: 14 initial implants and 34 replacements. The number of generators per patient varied between 1 and 8. Four children still had their initial implant after 13–73 months. The generator was changed for prophylactic reasons in 14 of the 34 replacements. Sudden generator failure occurred in four pacemakers. Generator change without lead change was required because of extrusion in two instances and infection in one. Competitive pacing of a ventricular fixed rate pacemaker was the reason for generator change in one case. In 12 cases non-generator related complications led to pacemaker replacement: (*a*) nine prophylactic replacements at the time of lead failure; (*b*) generator plus lead change because of infection in two instances; and (*c*) exit block treated by the insertion of a high output pacemaker in one case. Table 2 shows these data together with the length of life of the replaced pacemakers. The use of special paediatric pacemakers with only two mercury-zinc batteries was the reason for the early prophylactic changes and failures.

Cordis 323–543 leads were implanted in five patients (cases 1, 2, 3, 5, and 11) and Medtronic 5815A leads in five (cases 7, 8, 10, 12, and 13). Two patients (cases 6 and 14) were initially given a bipolar

Table 2 *Indications for pacemaker replacement and life of generators (in months). Figures are number of pacemakers*

	<30	*30–39*	*40–49*	*>50*	*Total*
Prophylactic change	4	1	3	6	14
Sudden failure	2	1	1	—	4
Lead problem	8	2	—	—	10
Extrusion	2	—	—	—	2
Infection	3	—	—	—	3
Competitive pacing	1	—	—	—	1
Total	20	4	4	6	34

General Electric epicardial electrode system, but subsequently these leads were replaced by Medtronic 5815A leads. In three patients it was necessary to replace the epicardial system by a transvenous one because of extrusion (case 6), exit block (case 7), and infection (case 14). In one patient (case 7) the system had to be changed back to an epicardial one after exit block of the transvenous system had occurred. In this instance, epicardial leads were implanted as well as a Hancock pulmonary valve prosthesis, as pulmonary insufficiency caused a high right ventricular stroke volume making adequate positioning of an endocardial lead impossible. In two patients (cases 4 and 9) transvenous endocardial leads were implanted as the initial system.

The initial lead system remained without malfunction in only seven patients. In the remaining seven patients 20 lead malfunctions occurred: lead fractures (6), insulation defects (3), exit blocks of epicardial leads (6), infection-extrusion (2), and exit blocks of endocardial leads (3). Lead fracture required a new lead implantation in three instances and could be overcome by the use of an additional lead on two occasions. One fracture occurred in a spare lead. Insulation defects required lead replacement in two cases, and on only one occasion could the defect be repaired. Because of exit block the epicardial leads had to be replaced in four instances; the pacemaker was replaced by a high output unit on one occasion. In one case the bipolar pacing was changed to the unipolar mode. Because of exit block two transvenous leads had to be repositioned, and in one patient the transvenous system was replaced by an epicardial one. In the two cases of extrusion-infection the old epicardial pacing system was completely removed and replaced by a transvenous one. A prepectoral position was chosen for the pulse generator in one case and an epigastric position in the other. Table 3 summarises the most important features of the complex history of these 14 children.

A spontaneous heart rhythm occasionally inhibiting the ventricular demand pacemaker was seen in only one patient (case 13). Absence of escape rhythm during pacemaker inhibition by chest wall stimulation occurred in six patients (cases 6, 7, 8, 9, 11, and 14). All these six patients had experienced Adams-Stokes attacks. Two patients with a previous history of Adams-Stokes attacks always had an adequate underlying heart rhythm (cases 2 and 5). During chest wall stimulation all patients who were asymptomatic before pacemaker implantation proved to have a reliable escape rhythm on all occasions (cases 1, 3, 4, 10, 12, and 13).

All these 14 children led a normal physical life and were psychologically well adjusted for their age and intellectual capacity. Excellent results at school were obtained by eight patients (cases 2, 4, 6, 8, 9, 11, 12, and 14). In one patient (case 7), who had recently started an administrative job, the presence of an isotopic pacemaker added to his confidence and that of his parents. In the children with an isotopic pacemaker in particular, the psychological effects of a pacemaker tended to disappear completely.

Discussion

Postoperative complete atrioventricular block was the major indication for cardiac pacing in our patients. We also treated three patients with congenital complete heart block and two with sick sinus syndrome. One patient with congenital heart block also had congenital heart disease. Similar cases are reported by other authors. In a French multicenter study Vanetti *et al* studied 241 children with permanently implanted pacemakers.[2] Congenitial complete heart block was found in 66 cases and was associated with congenital heart disease in a further 32, and 136 cases had postoperative heart block and seven acquired heart block. Young reviewed 448 pacemaker implantations in children.[3] In 284 cases pacemaker implantation was required as a result of intracardiac surgery; in 270 cases pacemaker implantation was required because of postoperative heart block which was not necessarily symptomatic and in 14 because of postoperative symptomatic sinus nodal dysfunction. Permanent pacing was undertaken in 137 patients with symptomatic heart block and in 27 with symptomatic sinus nodal dysfunction of idiopathic, congenital, or acquired (non-surgical) aetiology.

Numerous reports discuss the therapeutic dilemma in the case of congenital complete heart block. A benign prognosis has been reported by Campbell and

Table 3 *Surgical procedures*

Case No	*Year of first implantation*	*Surgical procedures (time between procedures in months*)*
1	1978	Initial implant of 2 epicardial leads—(7)—reintervention and use of reserve lead and elective generator replacement—(63)—generator replacement
2	1977	Initial implant of 2 epicardial leads—(58)—generator replacement—(24)
3	1982	Initial implant of 2 epicardial leads—(16)—reintervention and use of reserve lead—(7)
4	1983	Implantation of transvenous lead—(13)
5	1978	Initial implant of 2 epicardial leads—(73)
6	1972	Initial implant of General Electric epicardial lead system—(2)—elective generator replacement at time of lead complication—(14)—subsequent reintervention for implantation of 2 epicardial leads and replacement of generator—(1)—generator replacement—(4)—generator replacement—(8)—implantation of transvenous lead and replacement of generator—(1)—repositioning of transvenous lead—(26)—generator replacement—(50)—generator replacement—(41)—implantation of transvenous lead—(1)
7	1967	Initial implant of 3 epicardial leads—(10)—reintervention for implantation of 1 epicardial lead and replacement of generator—(30)—generator replacement—(38)—elective replacement of generator—(8)—reintervention and use of reserve lead—(4)—implantation of transvenous lead and replacement of generator—(20)—generator replacement—(1)—reintervention for implantation of 2 epicardial leads and generator replacement—(46)—generator replacement—(50)
8	1977	Initial implant of 2 epicardial leads—(50)—generator replacement—(37)
9	1971	Implantation of transvenous lead—(30)—repositioning of transvenous lead and generator replacement—(26)—generator replacement—(54)—generator replacement—(60)
10	1973	Initial implant of 2 epicardial leads—(31)—generator replacement—(44)—generator replacement—(50)
11	1980	Initial implant of 1 epicardial lead—(47)
12	1969	Initial implant of 3 epicardial leads—(13)—reintervention and use of reserve lead and generator replacement—(23)—generator replacement—(5)—generator replacement—(8)—reintervention and use of reserve lead—(33)—generator replacement—(58)—generator replacement—(37)
13	1968	Initial implant of 3 epicardial leads—(26)—generator replacement—(26)—generator replacement—(2)—death
14	1970	Initial implant of General Electric epicardial lead system—(11)—generator replacement—(4)—reintervention for implantation of 1 epicardial lead—(4)— reintervention for implantation of 2 epicardial leads and generator replacement—(5)—implantation of transvenous lead and generator replacement—(40)—generator replacement—(20)—death

*Until 31 August 1984.

Thorne.[8] They followed seven patients for 25 years and only one died. Only one had an enlarged heart and evidence of aortic regurgitation. Corne and Mathewson also emphasised the excellent prognosis in congenital complete heart block, provided that there is no associated congenital structural heart disease, that the QRS complexes are supraventricular in configuration, and that the condition is not familial.[9] Molthan *et al*, Ayers *et al*, and Nakamura and Nadas challenged the general belief that complete heart block has a good prognosis.[10-12] Molthan *et al* have reported three cases of fatal Adams-Stokes attacks in a series of 35 children with congenital complete heart block examined between 1953 and 1961.[10] Nakamura and Nadas found an unexpectedly high mortality of 21·3% (13 cases).[12] The severe disturbance in atrioventricular conduction, causing Adams-Stokes attacks, could clearly be indicated as the cause of death in only three patients. None of these patients died of the first attack; in fact, they all had at least three attacks. These workers emphasised that complete heart block not only causes death by Adams-Stokes attacks but may also worsen the prognosis of associated congenital heart disease. The patients who have slower rates, wide QRS complexes, previous Adams-Stokes attacks, and a poor response to exercise or drugs are those most likely to have a fatal outcome. Ayers *et al*[11] agreed with Nakamura that in any child with complete heart block who has had two or more Adams-Stokes attacks, permanent pacemaker treatment should be seriously considered. Karpawich *et al* suggested that the simple procedure of measuring heart rate at rest appeared to be the best current predictor of bradycardia induced syncope in young children with congenital complete heart block.[13] No child with a heart rate at rest of 50 beats/min or more had syncope, whereas seven of the 11 children with a lower heart rate had syncope. Karpawich *et al* recommended cardiac pacing in any child with symptoms attributable to Adams-Stokes attacks or congestive heart failure caused by a low heart rate. The greatest risk of death for the child with congenital heart block is in early infancy.[14]

In our patient group we had three cases of congenital complete heart block. All three had a pacemaker implanted. Two patients (cases 3 and 4) were asymptomatic but showed pronounced bradycardia and long ventricular pauses. Adams-Stokes attacks had occurred in one patient (case 5). In our view the indication for permanent cardiac pacing in these three patients was clear.

Postoperative complete heart block is generally considered to be a serious and life threatening condition. Murphy *et al* studied eight patients with postoperative complete heart block who were not given a pacemaker.[15] During a mean observation period of two years all were asymptomatic and none died. The follow up period of two years was possibly too short to allow a valid clinical judgement. Lillehei *et al*, McGoon *et al*, Sayed, and Liu *et al* have favoured the use of cardiac pacemakers for the long term management of postoperative complete heart block because of the high mortality rate in patients given medical treatment alone.[16–19] Hurwitz *et al* observed 13 children with chronic postoperative complete heart block; of these, 10 were not given a pacemaker and three of the 10 died.[20] The survivors were followed up for periods of eight months to nine years, but only three of the seven survivors did not experience Adams-Stokes attacks. Hofschire *et al* reported postoperative complete heart block in 64 children, some of whom were treated with cardiac pacing and some who were not.[1] Five of the seven patients with complete heart block who received medical treatment died after discharge from hospital. The authors proposed a policy of implanting a permanent pacemaker when complete heart block persisted for 4–6 weeks after operation. Forty seven of their patients with complete heart block survived the immediate postoperative period. In 23 (50%) regular sinus rhythm returned within four weeks after the operation.

Postoperative complete heart block accounted for nine cases in our series. All patients except cases 10, 12, and 13 experienced Adams-Stokes attacks. In the three asymptomatic patients we waited between 21 and 35 days before implanting a permanent pacemaker. In view of the poor prognosis of postoperative complete heart block we consider that a permanent cardiac pacemaker should be implanted in patients with complete heart block after intracardiac surgery when there is no restoration of normal atrioventricular conduction within a few weeks after the occurrence of complete heart block. The three asymptomatic patients with postoperative complete heart block always had a reliable underlying heart rhythm when their pacemaker was inhibited by chest wall stimulation.

The two children with sick sinus syndrome are the two paced patients of a series of five paediatric patients who have been extensively reported elsewhere.[6] One child survived sudden death and the other had extreme bradycardia and prolonged ventricular pauses.

Complications in a population of paced children are common. Premature battery failure, fracture of leads, infection, change in pacing threshold, arrhythmia, and pulse generator failure are reported in numerous series.[1–3 21–25] In our series only two patients received a transvenous pacing system as the initial implant. In the study of Vanetti *et al* 93·4% of the children had myocardial leads implanted.[2] Hayes *et al* reported that in their patients 13% of those with transvenous endocardial leads required a second operation compared with 35% of those with epicardial pacing.[22] In the patients with epicardial pacing reoperation involved a thoracotomy in 18%. We preferred to use epicardial leads in children because (*a*) we wanted to save the transvenous access for later life and (*b*) recovery after a small thoracotomy was always uneventful in children.

Gillette *et al* established clear criteria for transvenous pacing in children: they were (*a*) aged 4 years or more; (*b*) weighed 15 kg or more; (*c*) had no right to left shunt; (*d*) had adequate communication of a superior vena cava with at least part of an atrium; and (*e*) were not undergoing a simultaneous cardiac operation.[26]

Growth and lead stretch were not a major cause of failure in either transvenous or epicardial leads. One patient (case 9) to date has been paced by the same transvenous lead for 130 months. The persistent small size of this child is the reason for the absence of lead complications. In only one patient (case 6) was lead stretch the apparent cause of fracture in the transvenous lead. Fracture occurred after 118 months when the child had grown very tall.

Fracture of epicardial leads occurred after seven months (case 1), 16 months (case 3), 13 months (case 12), and four months (case 14). Lack of surgical skill and technical defects rather than growth and lead stretch are the most likely causes of failure after so short a period of time. To date well implanted epicardial leads have been functioning for 63 (case 1), 82 (case 2), 73 (case 5), 76 (case 7), 96 (case 7), 87 (case 8), 135 (case 10), 128 (case 12), and 54 (case 13) months.

Repositioning of the endocardial lead was necessary in two out of five patients who had received a transvenous lead (two initial and three subsequent implants). The complication of exit block or dislocation or both would probably have been prevented by the use of leads with active or passive fixation. To achieve maximum reliability and longevity of cardiac pulse generators, we now prefer to use isotopic pacemakers in young people. The benefits of the increased longevity of the lithium battery, which was initially very promising, are outweighed by the initial demands for a smaller size and later for more complex circuits. The longevity and reliability of the isotopic pacemaker have been found to be superior to pacemakers powered by chemical batteries.[27] Parsonnet *et al* reported on 151 atomic units implanted in 131 patients.[28] The survival of pacemakers after 10 years was 92%. This high reliability and superior performance suggest that the continued use of a radioisotopic power source is justified.

The short life of the pacemakers used in the first decade of paediatric pacing is shown in Table 2. Only six of the 34 replaced pacemakers functioned for 50 months or more. The limited life of mercury-zinc batteries together with the large size of their generators has played an important role in the complication rate. Attempts to manufacture small pacemakers with only one or two mercury-zinc batteries resulted in further shortening of longevity and a reduction in reliability.

Despite the high complication rate, pacing in children is a challenge that must be accepted by a pacemaker clinic. The long term follow up is a rewarding experience which is echoed by others.[24 25] Despite frequent admissions to hospital and pacemaker replacements paced children have normal physical development and psychological maturation. The important advances in equipment and techniques will largely improve the outlook for the future of paced children.

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Predictive value and limitations of the ST/HR slope

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SUMMARY To assess the value and predictive limitations of the exercise ST/HR slope, exercise test results were compared in 50 patients with stable angina and in 17 normal subjects with those in two groups known to have a high prevalence of inaccurate electrocardiographic responses to exercise. The last two groups included 51 patients tested within three weeks of acute myocardial infarction and 17 with important aortic regurgitation but no coronary disease. Of the normal subjects, 16 (94%) had ST/HR values $\leq 1{\cdot}1$ μV/beat/min. Of those with stable angina pectoris, 42 of 46 (91%) patients with coronary artery disease had ST/HR slopes ranging from 1·2 to 20·0 μV/beat/min, with false negative findings (slopes $\leq 1{\cdot}1$ μV/beat/min) in only four (9%). In contrast, of those with recent myocardial infarction, 15 of 42 (36%) with coronary disease had false negative slopes, including 12 of 20 (60%) with anterior wall injury. Of those with aortic regurgitation, conversely, 14 of 16 (88%) patients with calculable ST/HR slopes had values $>1{\cdot}1$ μV/beat/min despite the absence of coronary disease.

Despite the accuracy of the test in patients with stable angina, false negative results are common in those after recent myocardial infarction, and false positive results occur often in those with abnormal volume loading due to aortic regurgitation.

The rate related change in ST segment depression during exercise (the ST/HR slope) has been shown by Elamin *et al* and Kardash *et al* to identify accurately patients with coronary artery disease and to categorise patients with stable angina according to the extent of coronary disease.[1-3] In patients evaluated by treadmill exercise electrocardiography using a modified ST/HR slope analysis based on three electrocardiographic leads, we have found that this new method can improve the sensitivity, specificity, and predictive value of the exercise electrocardiogram for identifying three vessel coronary artery disease in patients with stable angina.[4]

Nevertheless, both the theoretical basis[5] and clinical applicability[6 7] of this technique have been challenged. Attempts by others to reproduce the perfect test accuracy of the ST/HR slope, using original bicycle exercise methodology, have been less successful,[6 7] and we have also found false positive and false negative test responses in relation to the extent of coronary disease that require further evaluation. To assess possible sources of error that might affect the applicability of the ST/HR slope as a test we compared the results in normal subjects (group 1) and patients with stable angina (group 2) with those in two groups of patients known to have a high prevalence of inaccurate electrocardiographic responses to exercise, those examined before hospital discharge after acute myocardial infarction (group 3) and those with important aortic regurgitation who had no coronary disease (group 4).

Patients and methods

GROUP 1

Seventeen normal subjects (including 16 men), whose mean (SD) age was 33 (12) (range 23–57) years, were selected from a clinically normal population with no history, symptoms, or signs of cardiac disease. None underwent coronary angiography. Nevertheless, each subject had a normal resting electrocardiogram and normal M mode echocardiogram.[8] In addition, each subject had a normal resting and exercise radionuclide cineangiogram,[9] with a >5% increase in left ventricu-

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lar ejection fraction during exercise and no evidence of localised wall motion abnormality. During standard exercise electrocardiography upsloping ST segment depression approaching 0·1 mV was present in two (12%) but none had horizontal or downsloping ST depression that reached 0·1 mV.[10]

GROUP 2

Fifty patients had stable angina pectoris (including 42 men and eight women) whose mean age was 53 (11) (range 31–74) years. Although 22 (44%) had had a previous myocardial infarction, in none had infarction occurred within two months of exercise testing. All patients underwent coronary angiography, and the extent of disease was graded according to the criteria used by Elamin *et al*.[2] Eighteen patients had three vessel coronary artery disease, including five with additional left main stem disease, 22 two vessel disease, six one vessel disease, and four no significant coronary disease. At the time of testing 28 (56%) patients were taking beta blocking drugs and two (4%) digitalis.

GROUP 3

Fifty-one patients had recent myocardial infarction (including 48 men and three women), whose mean age was 51 (10) (range 26–29) years. Each was examined as part of a routine predischarge assessment between 10 and 21 days after admission to hospital for acute myocardial infarction. Twenty-four patients had a recent transmural anterior wall myocardial infarction and 27 other types of infarction including 17 with a recent transmural inferior or true posterior wall infarction and 10 with a recent subendocardial infarction. All patients underwent coronary angiography: nine had three vessel coronary disease, 22 two vessel disease, 17 one vessel disease, and three no significant coronary disease. At the time of testing 11 (22%) were taking beta blocking drugs and five (10%) digitalis.

GROUP 4

Seventeen patients had aortic regurgitation (including 13 men and four women), whose mean age was 53 (14) (range 28–71) years. Each was studied as part of a longitudinal study of the natural history of valvar regurgitation. All these patients had haemodynamically important aortic regurgitation without additional valve lesions and were included because of the absence of coronary artery disease when examined at cardiac catheterisation because of symptoms or signs indicating a possible need for aortic valve replacement. At the time of testing one (6%) patient was taking beta blocking drugs and nine (59%) digitalis until three days before the test. Data were stratified for possible drug effects on the electrocardiogram.

EXERCISE ELECTROCARDIOGRAPHY

All exercise electrocardiograms were performed on a treadmill using standard or modified Bruce protocols.[11] Except in patients with recent myocardial infarction, in whom exercise was limited to 65–75% of maximum predicted heart rate, maximum heart rates were sought as the exercise endpoint. Tests were stopped if limiting chest pain, a fall in systolic blood pressure, three or more sequential ventricular extrasystoles, or limiting fatigue, dyspnoea, or dizziness occurred. Mean peak heart rates achieved were 177 beats/min in the normal subjects, 125 beats/min in patients with stable angina, 122 beats/min in those with recent myocardial infarction, and 153 beats/min in those with aortic regurgitation.

ST/HR SLOPE CALCULATION

The rate related change in ST segment depression (ST/HR slope) was calculated according to our previously reported modification[4] of the method developed by Elamin *et al* and Kardash *et al*.[1-3] The magnitude of ST segment depression, to the nearest 25 μV (1 mm=100 μV), was averaged in 3–4 complexes from a point 70 ms after the J point. ST segment measurements in leads aVF, V5, and V6 were related to heart rate, and the ST/HR slope was calculated from the linear regression data relating these variables. For each lead, the slope derived from linear regression analysis of the final three data points at peak exercise was compared with those obtained by including progressively earlier data. The highest slope with a statistically significant coefficient of linear correlation from among the three leads was selected as the test result. An upper limit of normal 1·1 μV/beat/min, as previously reported by Elamin *et al*,[2] was taken as accurately identifying normal subjects and those with stable angina pectoris. An ST/HR slope value of 6·0 μV/beat/min has previously been found to identify accurately patients with and without three vessel coronary disease among those with stable angina,[4] and agrees closely with the findings of Elamin *et al*.[1 2]

DATA ANALYSIS

Definitions of test sensitivity, specificity, positive predictive value, and overall accuracy conform to standard usage as previously reported.[4] Mean values are given with the standard deviation (SD) as the index of dispersion, and means were compared using Student's *t* test for unpaired samples. Proportions were compared using the χ^2 test with Yates's correction for continuity.

Results

The Figure shows the calculated exercise ST/HR

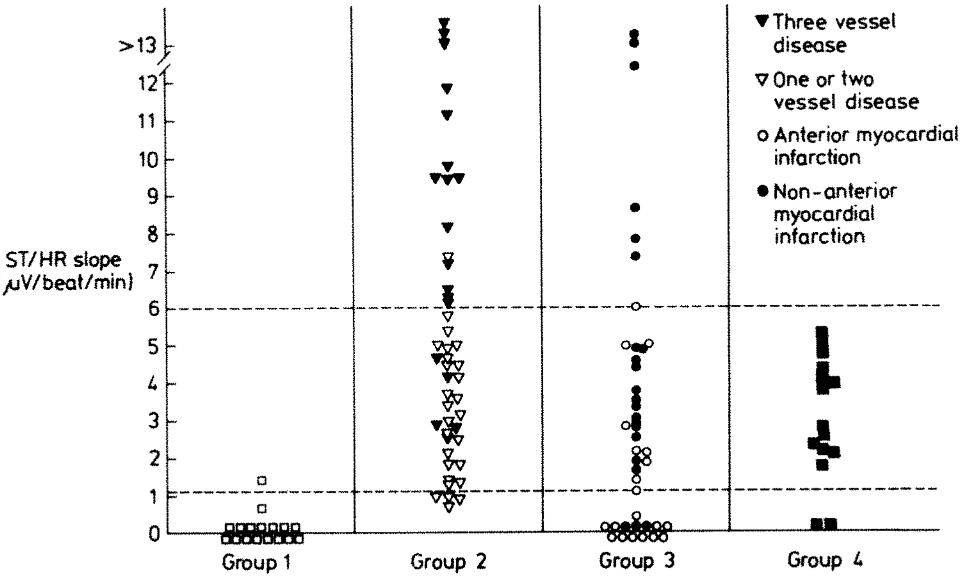

Figure *ST/HR slope in 17 normal subjects (group 1), 46 patients with stable angina pectoris (group 2), 42 patients with recent myocardial infarction (group 3), and 16 patients with aortic regurgitation (group 4). A slope of 1·1 μV/beat/min represents the upper limit of normal*[1 2] *and a slope of 6·0 μV/beat/min was used to identify three vessel disease.*[1 2 4] *(100 μV=1 mm.)*

slopes for all four groups of subjects. Using a value of 1·1 μV/beat/min as distinguishing between normal and abnormal ST/HR slopes in the normal subjects and in the patients with stable angina pectoris due to coronary disease resulted in a test sensitivity of 91% (42/46), a specificity of 94% (16/17), a positive predictive value of 98% (42/43), and an overall accuracy of 92% (58/63) in identifying coronary artery disease.

NORMAL SUBJECTS (GROUP 1)

A statistically valid ST/HR slope could be calculated for all the normal subjects. The mean ST/HR slope in this population was 0·12 (0·4) (range 0·0–1·4) μV/beat/min. The ST/HR slope was ≤1·1 in 94% (16/17) of these subjects.

PATIENTS WITH STABLE ANGINA (GROUP 2)

A statistically valid ST/HR slope could be calculated in all the patients with stable angina pectoris. In this group, 46 (92%) patients had significant coronary artery disease found at coronary angiography. The mean ST/HR slope in these 46 patients was 5·5 (4·4) (range 0·7–20·0) μV/beat/min. Of these, 42 (91%) had ST/HR slopes >1·1 μV/beat/min, while only four (9%) had ST/HR slopes ≤1·1 μV/beat/min.

PATIENTS WITH MYOCARDIAL INFARCTION (GROUP 3)

Of the 51 patients with recent myocardial infarction, 48 (94%) had coronary artery disease at angiography after exercise testing. In six (12%) patients no statistically valid ST/HR slope could be calculated owing to insufficient data points or to non-linear test responses, despite underlying coronary disease in each of these patients. Of the 45 patients with a calculable slope, 42 (93%) had coronary disease.

The mean ST/HR slope in myocardial infarction patients with coronary disease was 3·8 (5·6) (range 0·0–30·4) μV/beat/min. In contrast to patients with stable angina, ST/HR slopes ≤1·1 μV/beat/min were found in 15 (36%) of the 42 myocardial infarction patients with coronary artery disease during predischarge exercise testing ($p<0·005$). False negative values were particularly common among patients after acute transmural anterior wall myocardial infarction, of whom 12 (60%) had ST/HR slopes ≤1·1 and 10 (50%) slopes of 0·0 μV/beat/min. In contrast, ST/HR slopes ≤1·1 μV/beat/min occurred in only three (14%) of 22 patients with recent inferior or subendocardial myocardial infarction ($p<0·01$).

PATIENTS WITH AORTIC REGURGITATION (GROUP 4)

None of the 17 patients with aortic regurgitation had coronary artery disease at angiography. In one patient no statistically valid ST/HR slope could be calculated. Each of the remaining 16 patients had a calculable ST/HR slope (mean 3·1 (1·6) (range 0·0–5·3) μV/beat/min). False positive values were common in this group. Despite the absence of coronary disease, 14

(88%) patients with haemodynamically important aortic regurgitation had ST/HR slopes $>1\cdot1$ μV/beat/min compared with only one (6%) of the normal subjects ($p<0\cdot001$). Although over half the patients in this group had been taking digitalis until several days before testing, this could not be implicated as the cause of the false positive ST/HR responses. Mean ST/HR slope in the nine patients recently taking digitalis (2·9 (1·9) μV/beat/min) was no different from that in the seven patients not taking digitalis (3·3 (1·2) μV/beat/min, NS).

Discussion

Previous studies in Leeds[1-3] and in our laboratory[4] have shown that the ST/HR slope can significantly improve the accuracy of exercise electrocardiography in identifying and quantifying coronary disease in patients with stable angina pectoris. As predicted by Fox[5] and shown by Quyyumi *et al*[6] and by Balcon *et al*,[7] however, false positive and false negative test responses for the presence and anatomical extent of coronary disease can occur. This is in striking contrast to the perfect accuracy of the ST/HR slope reported by Elamin *et al* and Kardash *et al*.[1-3]

Our data suggest that conflicting reports of the applicability of this method might be partly explained by the relation of the ST/HR slope to factors other than the number of obstructed coronary arteries. Although our present findings confirm the ability of the ST/HR slope to distinguish patients with coronary disease and stable angina from normal subjects, it is also apparent that the ST/HR slope is often in the normal range in patients with recent myocardial infarction despite extensive coronary obstruction. Furthermore, we have found that the ST/HR slope is often significantly increased in patients with aortic regurgitation despite the absence of coronary disease.

It is well recognised that exercise electrocardiograms are commonly negative by standard test criteria after myocardial infarction,[12-14] and the ST/HR slope appears to be similarly limited in accuracy after infarction. False negative responses occurred most often after recent anterior wall injury partly owing to persistent ST segment elevation affecting the anterolateral leads. The applicability of the ST/HR slope after myocardial infarction was further reduced by the high prevalence of incalculable slope values. In contrast, statistically valid ST/HR slopes could be calculated in all patients with stable angina.

Conversely, false positive ST/HR slope responses might be predicted among patients with aortic regurgitation since standard exercise test criteria are often positive in patients with valvar heart disease who do not have coronary disease.[15 16] Indeed, most patients with aortic regurgitation had ST/HR slope values that were similar to the calculated slopes in our patients with coronary disease. Although some of our patients with aortic regurgitation had recently been taking digitalis, a drug effect cannot explain the electrocardiographic findings since identical changes occurred in the absence of digitalis.

Associated myocardial infarction, additional valvar disease, and a variable prevalence of three vessel disease must therefore be considered in the interpretation of apparently conflicting reports of the accuracy of the ST/HR slope.[1-4 6 7] We agree that perfect results[1-3] are unlikely with any test, but this issue should not obscure major improvements in overall test accuracy.[4] The patients studied by Quyyumi *et al*[6] were not characterised with regard to recent myocardial infarction or additional cardiac disease. Although Balcon *et al*[7] excluded patients with valvar disease from their study,[7] a substantial proportion of their population was reported to have previous myocardial infarction, including their only two patients who had three vessel coronary disease. We have also found an important overlap in ST/HR slope values in patients with one and two vessel disease.[4] Nevertheless, the unusually low prevalence of advanced coronary disease in patients reported by Balcon *et al* makes their findings potentially compatible with our finding that the ST/HR slope can improve recognition of three vessel disease in patients with stable angina pectoris.

Our findings therefore show that variability in the extent of the disease can appreciably affect the accuracy and applicability of the ST/HR slope. In ischaemic heart disease, the method appears to be most predictive in patients with stable angina pectoris. In the immediate postinfarction period the accuracy of the test is limited, perhaps because of discordant ST segment responses associated with recent injury and wall motion abnormalities in these patients. Among patients with non-ischaemic heart disease, it is reasonable to predict that further false positive ST/HR slope responses will be found with abnormal loading conditions in addition to aortic regurgitation. The predictive value of the ST/HR slope in hypertension and in the cardiomyopathies remains to be evaluated. We conclude that the patient population must be carefully selected in further evaluations of the ST/HR slope. In addition, the correlation of the ST/HR slope with geometric and functional variables may provide further insight into the mechanism of repolarisation changes in ischaemic and non-ischaemic heart disease.

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Right atrial embolus
Echocardiographic features

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SUMMARY Although the value of echocardiography in detecting left heart thrombus is well recognised, right atrial thromboembolism has rarely been identified in life. In two patients with pulmonary embolism of varying severity cross sectional echocardiography identified a thrombus moving freely within the right atrium and clearly showed its string-like or even tubular structure. An embolectomy, based on the echocardiographic diagnosis, was undertaken successfully in one patient. The value of routine echocardiography in patients with suspected pulmonary embolism is yet to be confirmed.

Intracardiac thrombus, a well recognised and important necropsy finding,[1] can now be identified in life by echocardiography.[2, 3] The ability of this technique to detect intracardiac thrombus in the left ventricle and left atrium is well described.[2, 3] Only two isolated case reports of the echocardiographic features of right atrial thromboembolism have, however, been reported.[4, 5] We report the echocardiographic findings in two patients with a mobile right atrial thrombus, in whom pulmonary embolism occurred. The M mode and cross sectional echocardiographic appearances in both cases were similar and form important and specific diagnostic criteria for the detection of right atrial embolus.

Patients and methods

CASE 1

A 59 year old West Indian man was admitted with sudden onset of breathlessness while climbing stairs at home. On examination he was apyrexial (temperature 36°C) and dyspnoeic at rest (respiratory rate 40/min) with a non-productive cough. His heart rate was 120 beats/min and his blood pressure 150/90 mm Hg, and the central venous pressure was not raised. The heart sounds were normal, but a soft and variable mid diastolic murmur was audible.

Chest radiographs showed a cardiothoracic ratio of 16:29 but no specific chamber enlargement, and the lung fields were clear. An electrocardiogram confirmed sinus tachycardia, a QRS axis of +90°, and poor R wave progression. The arterial pH was 7·4, $P\mathrm{CO}_2$ 32 mm Hg, and $P\mathrm{O}_2$ 62 mm Hg when the patient was breathing room air.

ECHOCARDIOGRAPHIC FINDINGS

Cross sectional and M mode echocardiograms were recorded using a Smith Kline Mechanical Echosector II. During routine M mode echocardiography of the right heart a normal tricuspid valve was clearly seen.

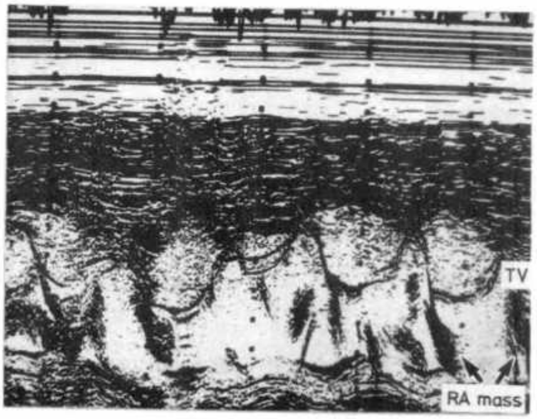

Fig. 1 *M mode echocardiogram (case 1) showing a normal tricuspid valve (TV) and a randomly moving mass within the right atrium (RA).*

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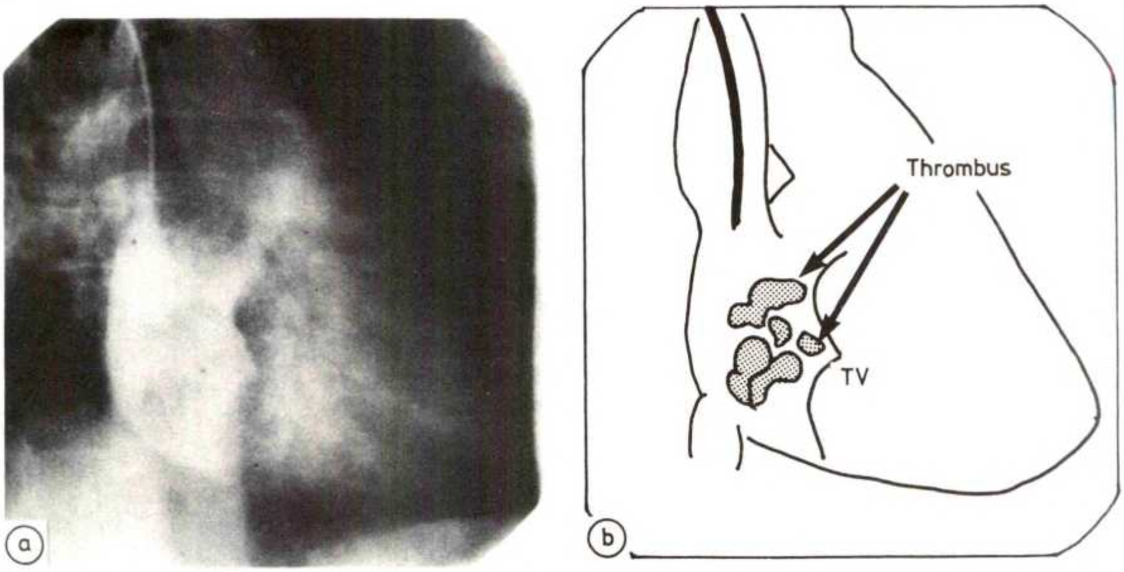

Fig. 2 *Right atrial angiogram (a) (case 1) with explanatory diagram (b) during systole showing a massive space occupying lesion within the right atrium. TV, tricuspid valve.*

Nevertheless, below this a randomly moving, echo reflecting mass approximately 1·0 cm in thickness was evident in the right atrium (Fig. 1). A cross sectional echocardiogram showed this same structure as a long coiled, string-like mass moving freely within the right atrium. The mass did not reflect the echoes strongly, so a high gain setting and low reject were necessary to visualise it clearly. Although well visualised in the short axis (at the aortic valve level), subcostal, and apical four chamber views, no clear point of attachment was apparent.

Additional findings

A lung perfusion scintigram showed filling defects in the left mid zone and right upper zone but a ventilation scan was normal. Right atrial angiography showed multiple large mobile filling defects that prolapsed across the tricuspid valve during diastole (Fig. 2). Subsequently, during preparation for surgery the patient collapsed and died. Postmortem examination confirmed a slightly enlarged heart (432 g) with mild left ventricular hypertrophy; the right ventricle was dilated but there were no intracardiac thrombi. Three major emboli were, however, removed from the pulmonary arterial tree, the most recent (22 cm in length) lay coiled astride the main pulmonary bifurcation (Fig. 3). Both lungs showed areas of peripheral infarction. Antemortem thrombosis was present in the veins of both calves and in the femoral vein on the left side only.

CASE 2

A 74 year old white woman had been unwell for several days with no specific symptoms. Two days before admission she had had an episode of acute breathlessness and had fainted. She also had a two year history of angina pectoris and palpitation. On the day of admission she had a two hour episode of severe central chest pain and breathlessness. On examination she was mildly breathless and not distressed. She was in atrial

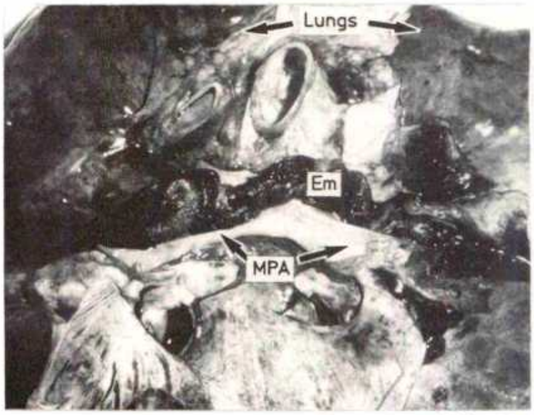

Fig. 3 *Morphological appearance of a massive embolus (Em) impacted in the pulmonary bifurcation (case 1). When uncoiled this (probable) venous cast was 22 cm in length. MPA, main pulmonary arteries.*

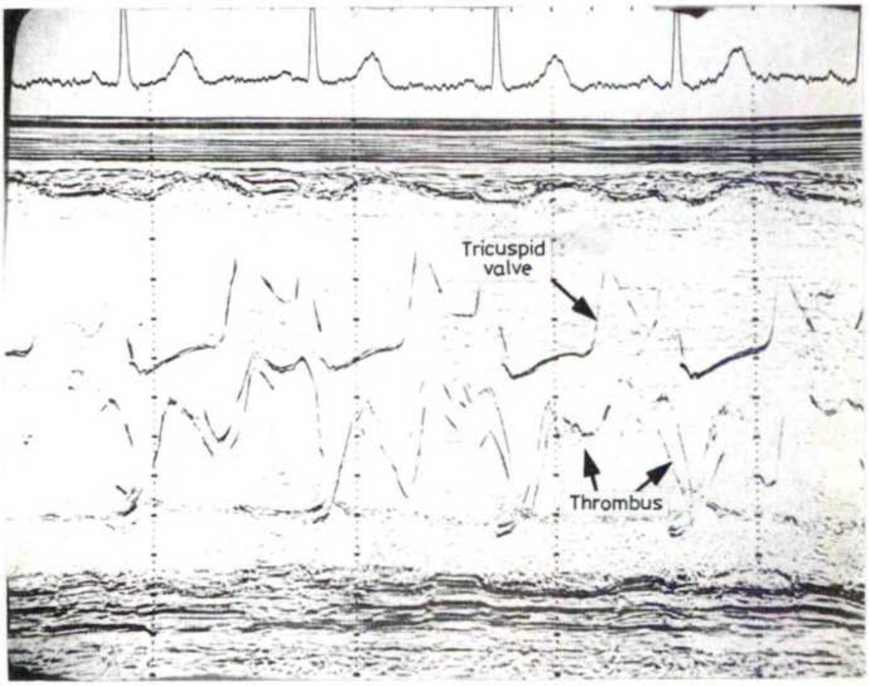

Fig. 4 *M mode echocardiogram (case 2) showing a normal tricuspid valve and a randomly moving thrombus posterior to it and within the right atrium.*

fibrillation with an apex rate of 130 beats/min; her blood pressure was 110/70 mm Hg and the heart sounds were normal. Her chest was clear, but she did have slight ankle oedema. An electrocardiogram confirmed uncontrolled atrial fibrillation and right bundle branch block. A chest radiograph showed upper lobe blood diversion.

She was initially thought to have had acute myocardial infarction, but early the next morning she complained of further breathlessness and chest discomfort. She became hypotensive (90/50 mm Hg), her venous pressure was raised, and there were signs of consolidation at the base of the left lung. A chest radiograph showed an effusion and collapse of the left lower lobe.

Echocardiographic findings

Cross sectional and M mode examinations were performed with a Hewlett Packard phased array ultrasound system. The M mode echo (Fig. 4) showed two parallel randomly moving echoes within the right atrium, which were separated by approximately 1 cm. As in the previous case, the cross sectional echocardiogram was more impressive, clearly showing a tubular structure approximately 1 cm in diameter and 4 or 5 cm in length moving freely within the right atrium but apparently attached at one end to the interatrial septum. Figure 5 shows an apical four chamber view in which the thrombus can be clearly visualised within the right atrium. In a parasternal modified short axis plane at aortic valve level the thrombus was visualised, in its own short axis, as a

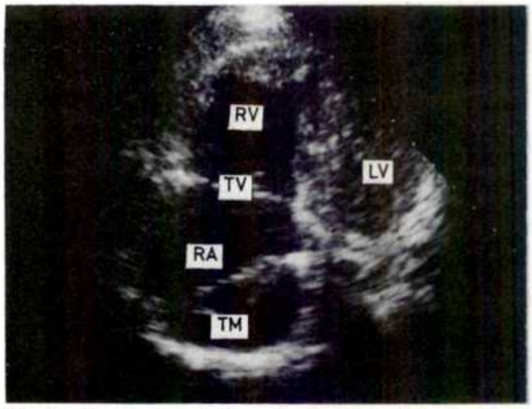

Fig. 5 *Cross sectional echocardiogram (case 2) in the apical four chamber view showing a tubular mass (TM) within the right atrium (RA). TV, tricuspid valve; RV, right ventricle; LV, left ventricle.*

ring-like object. These echocardiographic findings suggested the diagnosis of an embolised venous cast.

Additional findings
Based upon previous experience urgent surgery was advised. At operation an extensive thrombus was found in the right atrium and inferior vena cava. Pulmonary artery pressures were moderately raised (47/15 mm Hg), but no definite areas of pulmonary infarction were noted. The postoperative recovery was initially uncomplicated, but on the fourth postoperative day she had haemoptysis with further signs in the chest. A chest radiograph confirmed a new effusion and pulmonary collapse. Venography showed extensive left iliofemoral venous thrombosis. She was treated with urokinase and subsequently with warfarin. Recovery was uneventual thereafter.

Discussion

Although the clinical presentations of these two cases were slightly different, the echocardiographic features were strikingly similar. The characteristic appearance on M mode echocardiography was of an echo reflecting mass within the right atrium which moved randomly and was quite separate from a normal tricuspid valve. Although an early report related a massive pulmonary embolus to "dense shaggy echoes closely applied to the tricuspid valve",[5] the masses here were much less dense, clearly separated from the tricuspid valve, and much more like the recognised features of left atrial thrombus.[3] Important further detail was apparent on cross sectional echocardiograms which, in both cases, showed the object to be string-like (coiled or even tubular in form) and freely mobile; again it was not strongly echo reflective and therefore necessitated instrument settings of high gain or transmit and low reject or compression. Nevertheless, cross sectional echocardiography did not show a definite point of attachment. Importantly, there was no inferior vena caval extension.

There is little doubt that the echocardiographic masses were major emboli moving towards the lungs. In one patient (case 1) angiography confirmed a mobile right atrial mass that could only have been the massive thrombus found impacted in the pulmonary bifurcation at necropsy. Similarly, in the second case a thrombus was again clearly identified as the source of the characteristic echocardiographic appearance. Thus the characteristic features of a right atrial thrombus appeared to be those of a poorly echo reflective mass, usually with a string-like appearance moving randomly within the right atrium but with clear separation from the tricuspid valve and inferior vena cava. The mass should be visible in several cross sectional echocardiographic views to exclude the possibility of artefact.

The clear separation from the tricuspid valve excludes the possibility of vegetation or redundant valve apparatus. The acoustic properties, absence of stalk and point of attachment, and absence of paradoxical septal motion differentiate this mass from a myxoma.[6] The absence of pericardial effusion, involvement of the right atrial wall or one or other vena cava, and the low echo reflectance also exclude the possibility of primary or secondary tumour.[6] No previously reported features of congenital heart disease could account for these findings, although the vestiges of an inferior vena caval valve could be misinterpreted as a right atrial mass. Nevertheless, the characteristic features of the inferior vena caval valve, both the site and orientation of the echoes, and their "bright rotatory features"[7] are quite different from the structure described here and should alert the echocardiographer to this diagnosis.

Although the second patient appeared to have had several small pulmonary emboli, a major episode was probably prevented.Thus when massive pulmonary embolism is suspected such echocardiographic features might permit more urgent surgery and obviate the risks of pulmonary angiography.

While the overall incidence of two cases among approximately 4000 examined by routine echocardiography in a two and a half year period is low, the incidence among patients with suspected pulmonary embolism may be higher, and thus the potential value of routine echocardiography in such patients remains open to discussion.

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Immunogenicity and the vascular risk of oral contraceptives

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SUMMARY Data concerning circulating immune complexes were obtained for women who had had a pulmonary embolism, myocardial infarction, or cerebral thrombosis, and for 224 healthy controls. In women with pulmonary embolism who had used oral contraceptives concentrations of circulating immune complexes were significantly higher than in healthy controls (regardless of oral contraceptive use), or in those with pulmonary embolism who had never used these preparations. Concentrations of circulating immune complexes were not raised in myocardial infarction, but these women had major risk factors for ischaemic heart disease. The group of patients with cerebral thrombosis without risk factors tended to have high concentrations of circulating immune complexes.

The data provide some confirmation that immunological mechanisms may play a role in thrombotic episodes associated with oral contraceptives, expecially when they occur in the absence of risk factors for vascular disease.

The association between oral contraceptives and thrombosis is now well established. Initial case reports have been confirmed by epidemiological studies, and users of oral contraceptives appear to be at an increased risk of venous thromboembolism,[1–3] cerebral thrombosis,[2 3] and myocardial infarction.[2 4 5]

Oral contraceptives are well known to be associated with abnormalities of lipid and carbohydrate metabolism, which are in turn associated with an increased risk of ischaemic heart disease. It has been shown that the use of oral contraceptives is associated with changes in the coagulation and fibrinolytic systems.[6] In addition, changes in the structure of the vessel walls have been reported.[7] None of the metabolic and haematological disturbances has been shown to be predictive of clinical cardiovascular disease in oral contraceptive users. A case report of a 36 year old woman who used oral contraceptives described the association of pulmonary artery thrombosis and an antiethinyloestradiol monoclonal IgG. This combination of rare events suggested that an immunological mechanism might play a role in thrombosis among oral contraceptive users.[8] Further studies indicated that some oral contraceptive users developed circulating immune complexes that precipitate in 25% saturated ammonium sulphate and that may contain antiethinyloestradiol antibodies.[9 10] Laboratory methods were subsequently developed to test samples of venous blood for circulating immune complexes and antiethinyloestradiol antibodies.[11]

The purpose of this collaborative study was to apply these laboratory methods to a large population of women, with and without thrombosis, who were users and non-users of oral contraceptives. It was hoped that this would allow us to study further the precise role of circulating immune complexes in the aetiology of cardiovascular disease associated with oral contraceptive use and to estimate the potential value of measuring circulating immune complexes as a screening test for oral contraceptive users at high risk of thrombosis.

Patients and methods

STUDY POPULATION

We identified all women aged 15–44 years discharged from hospitals in the Oxford region, Gloucestershire, Wiltshire, and Bedfordshire during 1974–1979 with a

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Table 1 *Numbers (percentages) of cases excluded from the study after reviewing hospital records*

Insufficient evidence of diagnosis	122 (19)
Within four months of surgery, trauma, delivery, or during pregnancy	137 (21)
Died between admission and study	53 (8)
Underlying illness contributing to diagnosis	32 (5)
Notes missing or miscoded (for example, wrong diagnosis, age, sex)	89 (14)
Total excluded after reviewing hospital records	433 (67)
Cases considered to be suitable for study	210 (33)
Total cases reviewed	643

diagnosis of myocardial infarction (International Classification of Diseases (ICD) eighth revision, rubric 410), cerebral artery thrombosis (ICD eighth revision, rubric 433), or pulmonary embolism (ICD eighth revision, rubric 450). Having obtained the permission of the consultant, two of us (SAA and CP) reviewed the hospital case notes for each of the 643 women in order to assess their suitability for inclusion in the study and to collect data on cardiovascular risk factors. Objective diagnostic criteria were required for inclusion in the study and women were excluded for the reasons shown in Table 1. The majority of exclusions were of women who were coded as having pulmonary embolism but in whom either there was insufficient evidence of diagnosis (no confirmatory radiograph, electrocardiogram, or lung scan) or an association of the event with a predisposing factor such as surgery, trauma, pregnancy, or delivery.

We then approached the general practitioners of the 210 women who were considered suitable for inclusion in the study to obtain their consent for us to visit their patients. Five (2%) women were excluded at the general practitioner's request. Letters were sent to the remaining 205 women explaining the purpose of the study and seeking their cooperation. The provisional date for a home visit was given, and if they were willing to help with the study they were asked to let us know whether this was convenient. If not an alternative date was arranged. It was not possible to visit 72 (34%) women, either because we could not contact them or because they would have found a home visit inconvenient or unwelcome.

The remaining 133 women were visited at home and asked to complete a questionnaire providing information about past medical history, family history, smoking history, menstrual history, height, weight, and the use of oral conceptives and other hormones. A sample of 20 ml venous blood was collected into a plain glass container and stored at 4°C for 12 hours before spinning at 3000 rpm for 15 minutes. A 5 ml aliquot was then despatched to Paris for measurement of circulating immune complexes. The aliquots were transported in numbered plastic tubes, within cold storage containers to maintain the temperature at 4°C, and reached Paris within eight hours of leaving Oxford and within one week of being collected. Blood samples were not obtained for 19 (9%) women, either at their own request or because they were considered to be too ill. Thus complete data, including the results of the blood tests, were available for 114 women, 54% of those originally considered suitable for inclusion in the study.

CONTROL GROUP

As well as including these women, we also collected similar information and blood samples from 224 women without a history of thrombosis. These women were identified through general practitioners, family planning clinics, and the Oxford Regional Blood Transfusion Service, and came from the same health districts and in similar proportions to the 114 women with thrombotic disease. The controls were not selected randomly but chosen to include reasonable numbers of women who had a history of oral contraceptive use, both current users and ex-users, and women who had never used oral contraceptives. Thus our data cannot be used to provide evidence concerning the risk of cardiovascular disease associated with the use of oral contraceptive.

All blood samples were handled in a similar way, and each batch that was despatched to Paris could include aliquots from women in each group. The numbers were allocated randomly, and the laboratory tests were carried out without knowledge of the clinical details.

PROTEIN ANALYSIS

The laboratory methods are described in detail elsewhere.[12] Serum precipitation was achieved with 25% saturated ammonium sulphate incubated overnight at 4°C. Quantitative determinations of the precipitated proteins were carried out by Lowry's method and expressed as μg proteins/ml serum. The coefficient of variation of the method is 16%. A cut off point of 700 μg was estimated for the upper limit of normal according to a group of controls.[13] Analysis of these proteins showed two results. Firstly, they contained

Table 2 *Numbers of women by history of thrombotic disease and oral contraceptive use*

*Oral contraceptive**	*With thrombosis*	*Without thrombosis*
Current users	61	106
Past users	36	78
Never users	17	40
Total	114	224

*Current use is defined for women with thrombosis as use within the month before the thrombotic episode (regardless of total duration) and past use as use at any other time before that (regardless of duration). All women who suffered a thrombotic episode stopped using oral contraceptives after the diagnosis. For women without thrombosis the terms past and current were also used, the reference point being the time when the blood sample was taken.

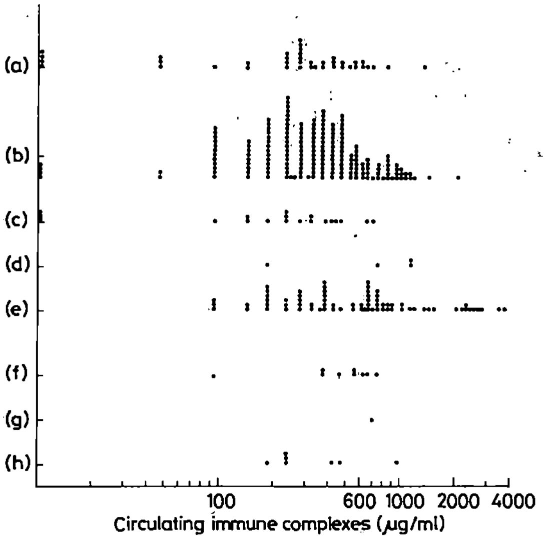

Figure *Circulating immune complexes in (a) healthy never users, (b) healthy ever users, (c) ever users with myocardial infarction, (d) ever users with cerebral thrombosis, (e) ever users with pulmonary embolism, (f) never users with myocardial infarction, (g) never users with cerebral thrombosis, and (h) never users with pulmonary embolism.*

almost exclusively immunoglobulins and complement fraction.[11] This protein content, together with the characteristics of precipitation in ammonium sulphate at 25% saturation, compared with 33% for normal unbound immunoglobulins, are consistent with circulating immune complexes. Secondly, in most cases[13] radioimmunoassays indicated that the precipitated immunoglobulins had binding activities for tritiated ethinyloestradiol by their Fab fragment, though even in oral contraceptive users the circulating immune complexes may contain antibodies to other ligands. The data were analysed using a statistical package for the social sciences.[14] The Wilcoxon test was used to determine the statistical significance of results.

Results

Complete data were obtained on 114 women with and 224 women without thrombotic disease. These two groups were subdivided for analysis into women who were current, past, or never users of oral contraceptives, as shown in Table 2. (For the study groups, current use is defined as use within the month preceding the thrombotic episode and for the controls as use at the time of blood collection.) The group of women wth thrombotic disease included 28 with myocardial infarction, six with cerebral artery thrombosis, and 80 with pulmonary embolism. All but three of the women with myocardial infarction had recognised risk factors for ischaemic heart disease, whereas none of the patients with stroke were known to have major cardiovascular risk factors—namely, hypertension, hyperlipidaemia, smoking, or diabetes.

The reproducibility of the measurements of the concentrations of circulating immune complexes was assessed by analysing two or three repeat samples at intervals on 11 women (seven with and four without thrombotic events) participating in the study. Except for a single high result in one patient, which was not confirmed on a repeat testing, the results showed consistency. The coefficient of variation was within that demonstrated for the method.

CONCENTRATIONS OF CIRCULATING IMMUNE COMPLEXES

The Figure shows the concentrations of circulating immune complexes plotted on a log scale for each subgroup (see Table 3 for data).

Healthy users and non-users

Concentrations of circulating immune complexes tended to be higher in healthy ever users of oral contraceptives than in women who never used the prep-

Table 3 *Concentrations of circulating immune complexes (CIC) in patients and healthy women*

Diagnostic category	*No of women*	*Concentration of CIC (µg/ml)*				
		Mean	*Median*	*SD*	*% of women with <700*	*% of women with >700*
Oral contraceptive users (either current or past):						
With myocardial infarction	19	276·3	240	201·4	100	—
With cerebral artery thrombosis	5	724·2	750	420·8	40	60
With pulmonary embolism	73	841·4	640	832·2	62	38
Healthy	184	418·6	379	296·9	86	14
Oral contraceptive never users:						
With myocardial infarction	9	496·6	552	194·6	89	11
With cerebral artery thrombosis	1	700·0	700	—	100	—
With pulmonary embolism	7	396·6	251	282·9	86	14
Healthy	40	345·5	282	267·6	95	5

SD, standard deviation.

arations, but the differences were not statistically significant. Healthy past users had higher concentrations (mean 463·3 μg/ml) than current users (mean 385·4 μg/ml), a difference which was not statistically significant. We are unable to explain this difference since concentrations were not related to the time since ceasing to take the pill. In no case was the pill withdrawn because of a major medical condition. This does not, however, invalidate any comparisons between women with and women without thrombotic events, for if the concentrations of the circulating immune complexes in healthy past users of oral contraceptives were higher it would have the effect of apparently weakening any association between a raised concentration of circulating immune complexes and pulmonary embolism.

Pulmonary embolism

The most interesting results were those obtained for the women admitted with pulmonary embolism. The concentrations of circulating immune complexes in these women with a history of oral contraceptive use were higher than in healthy users, and an appreciably greater number had values over 700 μg/ml ($p<0{\cdot}001$). Only seven of the women with pulmonary embolism had never used oral contraceptives and their concentrations were very similar to the healthy women; only one never user had a value greater than 700 μg/ml.

CONFOUNDING VARIABLES

These results suggest that a high concentration of circulating immune complexes is associated with pulmonary embolism in women who have used oral contraceptives. There are, however, several possible confounding variables which may be causing bias.

Age—Our data show an increase in concentrations of circulating immune complexes with age—for example, in the healthy women with a history of no oral contraceptive use there was a significant correlation between log concentrations of circulating immune complexes and age ($r=0{\cdot}576$, $p<0{\cdot}05$). Moreover, the women with pulmonary embolism were on average older than the healthy women (mean ages 35·6 and 30·2 years respectively). A separate analysis was therefore carried out for the 58 women who could be precisely matched with a control subject for age and oral contraceptive practice. Table 4 shows that for each age group the concentrations of circulating immune complexes were higher in the women with pulmonary embolism. Thus, although age is theoretically a confounding variable, it does not appear to explain the differences in concentrations of circulating immune complexes between women who have used oral contraceptives with and without pulmonary embolism.

Type of oral contraceptive—Our analysis considered not only user status—that is, current, past, or never—but also the duration of use and type of preparation. Interesting historical differences in types of preparations emerge owing to the fact that the women who had had thrombotic disease ceased to take oral contraceptives after their hospital admission; because of this far fewer study patients than healthy women had ever used preparations containing less than 50 μg oestrogen per day. Over three quarters of the healthy current oral contraceptive users had used these lower dose preparations compared with only one quarter of women with pulmonary embolism at diagnosis. Nevertheless, when the women were analysed in three subgroups—those who had a history of using oral contraceptives containing >50 μg, 50 μg, and <50 μg oestrogen—no consistent trend in concentrations of circulating immune complexes was found. The mean concentrations for all women included in the study were subdivided into three groups. When a similar analysis was carried out on the women with pulmonary embolism and the healthy women there was no evidence that oral contraceptives containing higher doses of oestrogen were more commonly associated with higher concentrations of circulating immune complexes. We did not attempt an analysis by specific preparation (the numbers would have been too small), but our data do not suggest that the dose of oestrogen is an important confounding variable.

Duration of oral contraceptive use—Comparison of

Table 4 *Concentrations of circulating immune complexes (CIC) in women with pulmonary embolism and healthy women matched by five year age group*

Age group	*No of women*	*Women with pulmonary embolism*			*Healthy women*		
		Lowest concentration (μg/ml)	*Highest concentration (μg/ml)*	*Mean concentration (μg/ml)*	*Lowest concentration (μg/ml)*	*Highest concentration (μg/ml)*	*Mean concentration (μg/ml)*
15–19	2	900	1460	1180	235	235	235
20–24	6	235	2540	1246	188	1170	611
25–29	8	329	1640	792	0	1130	378
30–34	18	188	2260	690	0	850	358
35–39	13	94	3840	888	0	564	293
40–44	9	188	2350	1014	94	1030	365
45–49	2	658	750	704	0	188	94

duration of use indicated that the healthy women tended to have taken oral contraceptives for slightly longer than the women with thrombotic disease, but these differences were not significant.

Time since thrombotic event—All groups of oral contraceptive users included current and past users. Thrombotic patients defined as current users all stopped taking oral contraceptives at the time of diagnosis, so that they might not have taken the preparations for several years before the time of sampling. Consequently it is conceivable that the concentrations of circulating immune complexes might have fallen since the time of stopping these preparations. This would, however, have resulted in patients with thrombosis having lower rather than higher concentrations than the healthy users. In fact, patients with thrombosis defined as past and current users had identical concentrations of circulating immune complexes, and these were not related to the time since stopping oral contraceptives.

Days to sending sample—The concentrations of circulating immune complexes were considered according to the number of days between collecting the sample and it arriving in Paris. The time interval was not found to have any effect on the concentration.

Myocardial infarction and stroke—There were no significant differences between the concentrations of circulating immune complexes in the women with myocardial infarction and their equivalent healthy controls. Of the 28 cases of myocardial infarction, all but one had concentrations <700 μg/ml. It may be relevant though that the great majority of these women (25) had other risk factors for ischaemic heart disease. The number of patients with cerebral thrombosis is very small, but it is of interest that this group, who did not have other cardiovascular risk factors, had high concentrations of circulating immune complexes.

Discussion

Our methodology makes the assumption that, in the women with cardiovascular disease, the concentrations of circulating immune complexes after the event are similar to those beforehand. None of these patients continued to take oral contraceptives after diagnosis and thus could not have developed higher concentrations of circulating immune complexes as a result of continuing exposure. Although it is conceivable that the event itself might have stimulated the production of circulating immune complexes, our data provide evidence that this is not the case: women who had suffered a thrombotic episode but who had not used oral contraceptives had concentrations of circulating immune complexes similar to those in the healthy group. The most striking finding from our study is the tendency of women who had had a pulmonary embolism and used the pill at some time to have higher concentrations of circulating immune complexes than either healthy oral contraceptive users or women who had had the condition but never used the preparations.

The small number of patients with cerebral thrombosis tended to have high concentrations, but those with myocardial infarction did not. At first appearance the data appear not to be entirely consistent with the earlier findings from Paris. In the earlier study high concentrations of circulating immune complexes were found, regardless of the site of the thrombosis, in women using oral contraceptives.[10] The inconsistency is, however, almost certainly explained by the difference in case selection. The first series of cases studied in Paris were characterised by the absence of predisposing factors for vascular disease.[10] In the present epidemiological study patients were unselected with regard to predisposing factors. All those with myocardial infarction had cardiovascular risk factors and did not appear to have raised concentrations of circulating immune complexes. On the other hand, the stroke patients did not have risk factors and appeared to have higher concentrations, but numbers are too small to draw definitive conclusions. Having excluded pulmonary embolus in association with pregnancy, surgery, and trauma, we were left with a group without known risk factors for the condition. This explanation is supported by a current study of unselected patients in Paris,[13] which has shown a pattern of concentrations of circulating immune complexes similar to that observed in our study.

The healthy oral contraceptive users in our study appear to have higher concentrations of circulating immune complexes than similar women studied in France,[13] the difference being entirely due to the higher concentrations in past users. The current users have an almost identical mean concentration to those studied in Paris, and we are unable to explain the relatively high concentrations in our series of past users. This finding, together with the considerable overlap between various groups, makes it difficult to define from the present data a cut off point below which concentrations of circulating immune complexes might be considered as normal or above which they might be considered as abnormal.

The present data (derived from an unselected population in another country), however, do provide confirmatory evidence for the suggestion that an immunological mechanism may play a role in thrombotic episodes associated with oral contraceptive use, especially in women in whom these occur in the absence of risk factors for vascular disease. Refinement of laboratory procedures and prospective studies will be necessary to assess whether it is possible to define a cut off point and whether it would be of value to use measurements of circulating immune complexes as a screening test for vascular complications in oral contraceptive users. The present data are encouraging.

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Evaluation of lay skills in cardiopulmonary resuscitation

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SUMMARY The theoretical knowledge and practical performance of 166 lay people attending a short cardiopulmonary resuscitation course were evaluated according to the American Heart Association standards. Before tt course no participant was able to perform even a bad attempt at cardiopulmonary resuscitation. Theoretical knowledge was good at the end of the course and at the refresher course six months later. At the end of the initial course 65% (57/88) of the participants examined could adequately compress and ventilate the manikin. After six months 44% (30/68) could perform resuscitation adequately. Women were as proficient as men, and elderly people in general were as proficient as the younger ones. The skill of carotid artery palpation was surprisingly well retained after six months. Data on pulmonary ventilation and cardiac massage were recorded simultaneously on a recording resuscitation manikin. When these objective data were compared with the American Heart Association standards only a few participants were able to perform correct cardiopulmonary resuscitation. The number of compressions and ventilations per minute were often insufficient. A large discrepancy between self, subjective, and objective assessment of cardiopulmonary resuscitation knowledge and performance was found.

The importance of a rapid diagnosis, an immediate call for help, an adequate rate of cardiac massage, and a reduction in the time needed for ventilation should be emphasised at these courses. Refresher courses should be provided at least twice a year.

Since Kouwenhoven published his article on closed chest cardiac massage in 1960[1] cardiopulmonary resuscitation has been used by doctors and later by more and more lay people in cases of cardiopulmonary arrest. Both doctors and non-medical personnel have had to be trained in the technique of resuscitation. In 1974[2] and 1980[3] the American Heart Association published training programmes and guidelines.

To date more than 12 million adults in the USA have received instructions in cardiopulmonary resuscitation according to the American Heart Association standards. In the Netherlands (14·6 million inhabitants) several hundred thousand adults have been trained under the guidance of the Netherlands Heart Foundation (J van Drenth, personal communication). Only a few reports are available about the results of training lay people in cardiopulmonary resuscitation and about how well knowledge and practical performance are retained after some time.[4–7]

We evaluated the theoretical knowledge and practical performance of lay people before and after instruction in cardiopulmonary resuscitation and compared the results with those after six months to determine how well these skills had been retained.

Subjects and methods

CARDIOPULMONARY RESUSCITATION COURSE

By advertising in regional papers and with the aid of the local branch of the Netherlands Heart Foundation, the citizens of Nijmegen—a university city with 140 000 inhabitants—and its surrounding villages were invited to attend a cardiopulmonary resuscitation course. The course consisted of three evening sessions of theoretical and practical instruction. A fourth evening was designated for a 20 multiple choice questionnaire to evaluate theoretical knowledge. The practical cardiopulmonary resuscitation performance was evaluated by one of the instructors.

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A doctor gave two one hour lectures on the theoretical principles of cardiopulmonary resuscitation. The practical instructions were given by paramedical cardiopulmonary resuscitation instructors and consisted of four one hour sessions using a non-recording Resusci Anne manikin. All participants received an illustrated instruction booklet, which gives comprehensive information on cardiopulmonary resuscitation.[8] If the candidate completed the course and passed both the theoretical and practical tests, a certificate of proficiency was given with the date of the refresher course printed on it. Every six months three identical refresher courses consisting of 50 minutes of theoretical and 50 minutes of practical instruction were provided.

STUDY

During the study period from September 1982 until March 1984, 10 participants were randomly selected at the beginning of the course, 88 at the end of the course, and 68 before the start of the refresher course. All these participants were asked to answer a multiple choice questionnaire on diagnosis, pulmonary ventilation, and cardiac massage. Throughout the study they had to estimate their own level of theoretical knowledge and practical performance on a 1–10 scale. In addition, they performed cardiopulmonary resuscitation on a recording manikin (Laërdal Recording Resusci Anne, Asmund Laërdal, Stavanger, Norway) for at least two minutes to assess their performance objectively. Their practical performance was also judged subjectively by one of us and was scored on the following items: *(a)* psychomotor performance (establishing unresponsiveness, checking both carotid arteries, checking breathing, checking mydriasis); *(b)* adequate call for help (correct phone number and diagnosis); and *(c)* adequate performance of cardiopulmonary resuscitation (position of the hands, massage technique, massage rate, overstretching of the head, depth of ventilation, leakage of air).

Practical performance assessed by subjective data was considered as adequate when the participant could palpate the carotid artery on both sides of the manikin and perform about 15 cardiac compressions at a rate of 50–70/minute with adequate depth and two ventilations with adequate volume between two massage cycles.

The objective data from the recording manikin tape were analysed afterwards. Data on massage and ventilation were derived from the last full minute recorded, and comprised: *(a)* time from "go ahead sign" until first act of cardiopulmonary resuscitation; *(b)* number per minute and depth of compressions (standard 50–70/minute and 38–51 mm respectively); *(c)* number per minute and depth of ventilations (standard ≥5/minute, 0·8–1·6 l respectively); *(d)* rate of compressions (standard 70–90/minute); and *(e)* total time per minute (in seconds) needed for ventilation (the time between two massage cycles was recorded). In addition the ability to palpate and count correctly the instructor's carotid artery pulse on both sides was assessed.

Practical performance assessed by objective data was considered adequate when the examiner's carotid artery was correctly palpated ≤1 minute, the manikin was ventilated ≥5 times/minute with volumes of 0·8–1·6 l, and 50–70 cardiac compressions/minute were performed with a depth of 38–51 mm.

In the three groups the self estimated knowledge and practical performance of the different skills were compared with the subjective and objective assessments. Data were analysed by the university mathematical statistical department.

Results

POPULATION

From 1979 to 1984, nearly 3000 people attended their first cardiopulmonary resuscitation course in Nijmegen. Fifty six per cent came from the main town and 44% from the surrounding villages. The Figure shows the age and sex distribution of the total population. There were 73% women and 27% men. The mean age was 38 (range 13–73) years. Of those who

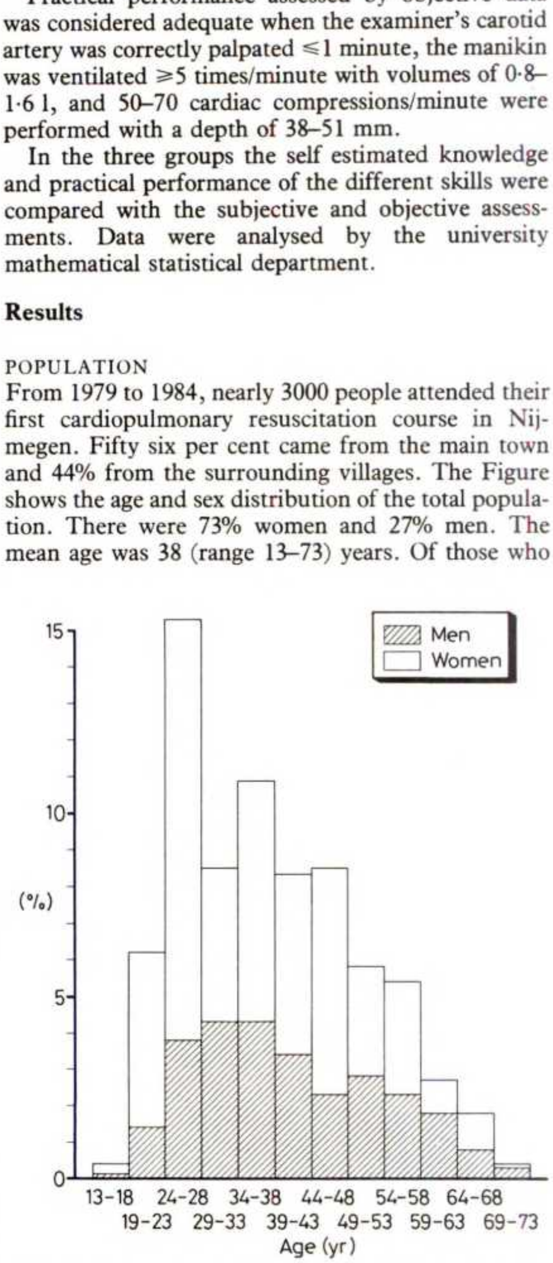

Figure *Age and sex distribution of participants attending a cardiopulmonary resuscitation course between 1979 and 1984.*

Table 1 *Age and sex distribution of the participants in the study before and after the course and at the refresher course*

	No of participants	*Women*	*Men*	*Mean (SD) age (yr)*		*No of participants aged*	
				Women	*Men*	*≤40 yr*	*>40 yr*
Before	10	7	3	34 (12)	38 (12)	5	5
After	88	56	32	37 (11)	38 (10)	63	25
Refresher course	68	38	30	36 (9)	42 (2)	48	20
Total	166	101	65	35 (11)	38 (11)	116	50

attended the course, only 30% returned at the first refresher course; this proportion decreased to 12% for those attending a fifth refresher course after two and a half years. Table 1 shows the age and sex distribution of the study groups. There was no difference between each of the groups and the total population regarding age and sex distribution. Most people attended the course because of social motivation and a few because of illness in their family.

THEORETICAL KNOWLEDGE

Theoretical knowledge was evaluated by the multiple choice questionnaire, and was considered adequate when more than 70% of the questions were answered correctly. Before the course theoretical knowledge was inadequate in all the participants but at the end of the course and before the refresher course this was good in both groups (Table 2), although a slightly lower figure was recorded at the refresher course. At the refresher course, a discrepancy was noted between self assessment and objective assessment scores. There was no difference in theoretical knowledge between older and younger people.

PRACTICAL PERFORMANCE

Subjective data

Before the cardiopulmonary resuscitation course when the participants were asked to help someone who had suddenly collapsed, none knew how to establish a proper diagnosis of cardiopulmonary arrest or how to perform adequate ventilation or massage or both (Table 3).

By the end of the course cardiopulmonary arrest was correctly diagnosed by 74% of participants but at the refresher course only 50% managed to do so. The call for help was given immediately after establishing a diagnosis by only 55% at the end of the course and by 46% at the refresher course, but 88% and 70% respectively achieved this within one minute after starting cardiopulmonary resuscitation. Ventilation was correctly performed by 20% of the participants before the cardiopulmonary resuscitation course, by 51% at the end of the course, and by only 37% at the refresher course.

Only 35% and 38% of participants respectively could correctly perform cardiac massage at the end of the course and at the refresher course. Too slow a rate was the most frequent fault in 35% and 40% of participants respectively at the end of the course and at the refresher course. A subjective assessment of adequate cardiopulmonary resuscitation at the end of the course and at the refresher course was thus performed in 65% and 44% of participants respectively, which contrasts with figures of 94% and 82% by self assessment. If the time since the last course was more than one year, the proportion fell further to 38% at the refresher course.

Objective data

At the end of the course and at the refresher course the mean time from the "go ahead" sign to the first act was 42 s (range 10–127, 90% between 15–80 s), but in both groups it took two candidates two minutes before they actually started cardiopulmonary resusci-

Table 2 *Percentage of participants in whom theoretical knowledge was assessed as adequate before and after the course and at the refresher course. Figures in parentheses are numbers of subjects*

	Before (n = 10)	*After (n = 88)*	*Refresher course (n = 68)*
Skills tested:			
Diagnosis	20 (2)	67 (59)	66 (45)
Ventilation	0 (0)	38 (33)	22 (15)
Massage	0 (0)	68 (60)	21 (14)
Objective assessment	10 (1)	93 (82)	71 (48)
Self assessment	20 (2)	93 (82)	94 (64)

Table 3 *Percentage of participants in whom practical performance was assessed as adequate before and after course and at refresher course. Figures in parentheses are numbers of subjects*

	Before (n = 10)	*After (n = 88)*	*Refresher course (n = 68)*
Skills tested:			
Diagnosis	0 (0)	74 (65)	50 (34)
Ventilation	20 (2)	51 (45)	37 (25)
Massage	0 (0)	35 (31)	38 (26)
Subjective assessment	0 (0)	65 (57)	44 (30)
Self assessment	0 (0)	94 (83)	82 (56)

Table 4 *Objective assessment of performance of participants in carrying out pulmonary ventilation and cardiac massage before and after the course and at the refresher course. Figures are percentages with numbers of subjects in parentheses*

	Before (*n* = *10*)	*After* (*n* = *88*)	*Refresher course* (*n* = *68*)
Pulmonary ventilation			
≥5 ventilations/minute	0 (0)	64 (56)	38 (26)
Adequate volume (0·8–1·6 l)	0 (0)	35 (31)	34 (23)
Time taken for two ventilations:			
<6 s	— (—)	25 (22)	12 (8)
6–10 s	— (—)	45 (40)	40 (27)
>10 s	— (—)	30 (26)	48 (33)
Adequate ventilation	0	48	28
Cardiac massage			
No of compressions/min (50–70/min)	0	25	22
Rate (70–90/min)	0	42	40
Depth (38–51 mm)	25	32	50
Adequate massage	0	5	3

tation. At the end of the course and at the refresher course 90% and 83% respectively were able to palpate the carotid artery ≤1 minute, two thirds of them succeeding within half a minute.

Table 4 gives details of the ventilation technique. Before the course the participants had no knowledge of ventilation. By the end 64% were able to give five or more ventilations in the last recorded minute, but only 35% were ventilating with adequate volume (0·8–1·6 l). At the refresher course only 38% ventilated ≥5 times per minute, again only one third ventilating with adequate volume. The mean time needed for two "quick" ventilations varied from 8 s (range 4–24 s) to 10 s (range 6–43 s) respectively; 30% at the end of the course and 48% at the refresher course needed more than 10 s.

Table 4 also gives details concerning cardiac massage. Before the course no participant could massage properly. Only about 25% of both groups delivered 50–70 compressions/minute, although 42% of the participants did this at an adequate rate. A high proportion of both trained groups (95% and 97% respectively) could not perform massage adequately.

COMPARISON OF ASSESSMENTS

Finally, we compared the participants' own assessment, the assessment by the instructors at the end of the course, the subjective assessment (by one of us), and the objective assessment derived from the recorded tape (Table 5). The data on diagnosis are missing, because they were not recorded on the tape. When the American Heart Association criteria are strictly applied only 7% and 1% respectively in both groups were able to perform correct cardiopulmonary resuscitation.

Table 5 *Percentage of participants performing adequate cardiopulmonary resuscitation before and after the course and at the refresher course by self assessment, instructors' assessment, subjective assessment, and objective assessment*

Assesement	*Before* (*n* = *10*)	*After* (*n* = *88*)	*Refresher course* (*n* = *68*)
Self	0	94	82
Instructors'	0	90	85
Subjective	0	65	44
Objective	0	7	1

Discussion

The number of people attending refresher courses is astonishingly low. Because most of these participants are well motivated and interested, a bias in the data obtained in this group is inevitable, and "improves" the results. Before the course no participant was able to perform even a bad cardiopulmonary resuscitation. After the three evening sessions theoretical knowledge was good and was well retained at the refresher course. Since, however, people knew the date of the re-examination and would have studied our instruction booklet at home the actual level of knowledge may have been even lower.

The technique of palpating the carotid artery was surprisingly well retained after six months. The mean time needed to diagnose cardiopulmonary arrest was 42 s in both groups, which is quite long even when the time needed to palpate the carotid artery on both sides of the manikin to ensure that there is no pulse (at most 20 s) is taken into account. The most common mistake in ventilation was the low number of ventilations/minute or an inadequate volume or both. Ventilation was notably worse when performed by people with dental prostheses since they generally leaked air; they performed better with mouth to nose ventilation. Some of the participants ventilated the manikin while chewing chewing-gum; this was discovered afterwards in the trachea of the manikin. Comparable events were reported by Shih *et al.*[9] In cardiac massage the most common fault was the low number of compressions performed per minute. The reason for this finding is not always an incorrect rhythm but the time needed for ventilation, together with the time needed to search for the correct compression point, reduces the time available for massage.

At the end of the course and at the refresher course there was a large discrepancy between the candidate's own estimation of their performance (98% and 82% thought themselves proficient), the assessment by the paramedical instructors (90% and 85% respectively), the subjective assessment (65% and 44% respectively), and the objective assessment using recorded tape data (7% and 1% respectively). The most objective method of examining candidates on their cardiopulmonary resuscitation performance is therefore by using recording manikins, since subjective criteria grossly overestimate the practical performance level. Nevertheless, these objective figures are also exaggerated since ventilation with a volume of 0·7 l or 1·8 l is sufficient for cardiopulmonary arrest, as is a cardiac compression rate of 49 or 72 compression/minute. Our results agree wth those of Ramirez *et al* and Weaver *et al*,[4 6] but Mandel *et al* described opposite results.[7]

In our community we give a three session course; even so we cannot claim satisfactory results when the lay participants are re-examined. It would be worthwhile to compare our results, especially those after the refresher course with those obtained after a course held within three hours, as is the instruction method for instance in Seattle.[10] Despite the problems and possible disappointing results, it is well known that cardiopulmonary resuscitation by lay people does save lives[11] and improves the neurological outcome.[12] In our forthcoming courses more attention will be paid to (*a*) the diagnosis (reduction of the time needed for checking the conscious level and palpation of the carotid artery, which with training can be done within 30 s); (*b*) call for help (to perform this immediately after the diagnosis of cardiopulmonary arrest has been established); (*c*) ventilation (to decrease the time taken for two ventilations and especially the time most people need to find the correct pressure point on the chest); and (*d*) massage (to increase the rate to 80 compressions/minute and to emphasise further the correct depth needed). It is advisable to provide refresher courses for lay people in cardiopulmonary resuscitation at least twice a year giving special attention to the above techniques.

We thank Mr Ph van Elteren and Mr A G M Dinkhuijsen for carrying out the analytical work. Part of this study was supported by a grant from the Netherlands Heart Foundation.

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Case reports

Diagnosis of pseudoaneurysm of the ascending aorta by pulsed Doppler cross sectional echocardiography

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SUMMARY Pseudoaneurysms of the ascending aorta are relatively uncommon compared with those evolving from the left ventricle. In a young man with endocarditis of the aortic valve who developed a pseudoaneurysm arising from the ascending aorta, the diagnosis was established with the pulsed Doppler technique and cross sectional echocardiography by passing the Doppler sample from the aorta through the neck of the false aneurysm into the large pseudoaneurysm. Aortic root angiography showed this connexion to be a small fistula between the aorta and right atrium. Necropsy findings confirmed the diagnosis.

Pseudoaneurysm of the ascending aorta is a rare entity. False aneurysms have a tendency to early and late rupture, necessitating early diagnosis and prompt surgical intervention. Until recently, only angiographic evidence of the small connexion between the false aneurysm and true aortic lumen could confirm the diagnosis. To our knowledge, there has been only one report that describes the use of pulsed Doppler cross sectional echocardiography in confirming the diagnosis of pseudoaneurysm. Grube *et al* were able to pass the Doppler sample through the communicating neck of a false aneurysm of the left ventricle while constantly monitoring flow.[1] We present here a most unusual case of a massive pseudoaneurysm of the ascending aorta diagnosed by combined echocardiography and the Doppler technique.

Case report

A 37 year old, previously healthy white man developed chronic osteomyelitis of the right leg after being struck by a car. He presented with *Staphylococcus aureus* endocarditis of the aortic valve. A Björk-Shiley aortic prosthesis and appropriate antibiotic treatment adequately relieved his symptoms. Several months later, he presented with recurrent signs of endocarditis and a loud murmur of aortic regurgitation. *Staphylococcus epidermidis* endocarditis with dehiscence of the aortic prosthesis was diagnosed. At operation, the aortic annulus was necrotic with one abscess. An Edwards porcine prosthesis was inserted with Dacron reinforcement of the ascending aorta. In the immediate postoperative period, he developed sharp substernal chest pain radiating to the back which was associated with a harsh systolic ejection murmur at the second right intercostal space. The pain became progressively more severe and was associated with tenderness in the fourth right intercostal space. There was a well localised pulsation in this area associated with both a systolic murmur and a diastolic decrescendo murmur. An echocardiogram was performed followed by cardiac catheterisation.

Cross sectional echocardiography (Fig. 1) detected a large mass anteriorly which compressed the right heart and ascending aorta. The right ventricle and right atrium were clearly defined as narrow distorted cavities, and the tricuspid valve showed an extremely erratic motion pattern. Careful examination along the right sternal border detected a small communication between the large anterior mass and the adjacent ascending aorta (Fig. 1b).

Pulsed Doppler echocardiography (Fig. 1b) was performed on an ATL Mark V pulsed Doppler instrument with a zero crossing time interval histogram spectral display of velocity. Flow profiles within the mass and ascending aorta showed a similar direction, but flow within the mass was much more turbulent. Furthermore, the Doppler sample passed easily through the communication of these structures and

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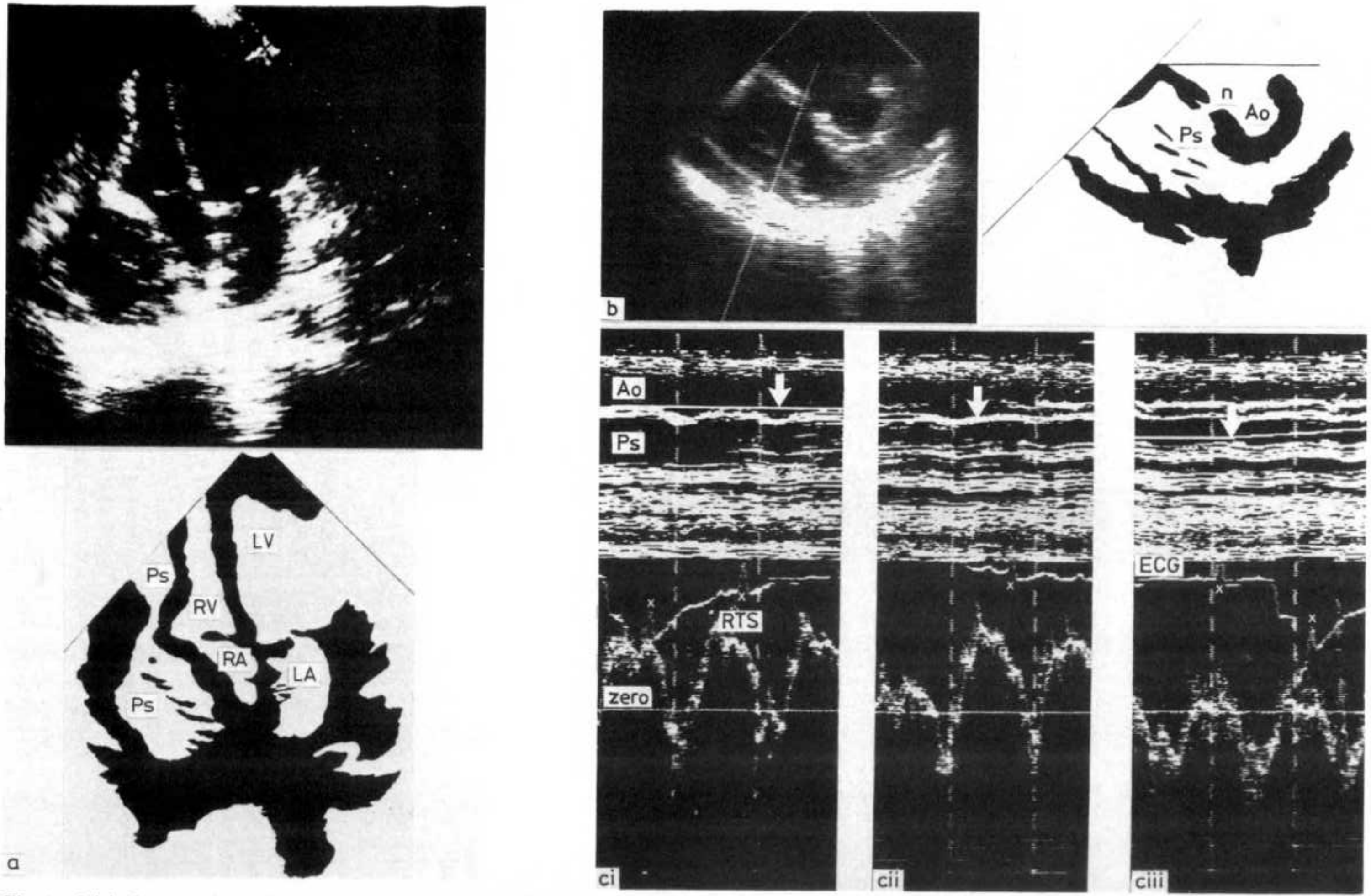

Fig. 1 *Original cross sectional echocardiograms (a) in the apical four-chamber projection (with corresponding diagram) showing a massive pseudoaneurysm (Ps) compressing both the right atrium (RA) and right ventricle (RV) (LV, left ventricle; LA, left atrium) and (b) in the right parasternal view (with corresponding diagram) showing the ascending aorta (Ao), the neck of the false aneurysm (n), and the pseudoaneurysm (Ps). (c) Real time spectral analysis of the Doppler shift frequency (RTS) is shown below the M mode recording with flow toward the transducer shown above the zero velocity line (zero) and flow away from the transducer shown below the zero line; the path over which the continuous sample volume was obtained is indicated in (c) by the depth line (arrow). The flow profile is analysed with reference to the electrocardiogram (ECG), in which each QRS complex is indicated (X). In (ci) the sample volume is in the aorta and shows a similar spectral pattern as seen in (cii) with the sample volume positioned in the neck of the false aneurysm. Note that systolic flow is away from the transducer and toward the pseudoaneurysm, but in diastole flow is out of the aneurysm and toward the transducer. In (ciii) the sample volume is within the false aneurysm and shows a wide variance in the velocity waveform with a much larger negative component in systole. This indicates turbulence within the aneurysm as the red blood cells have a variable direction and velocity which produces a spectral display with a widely dispersed dot pattern.*

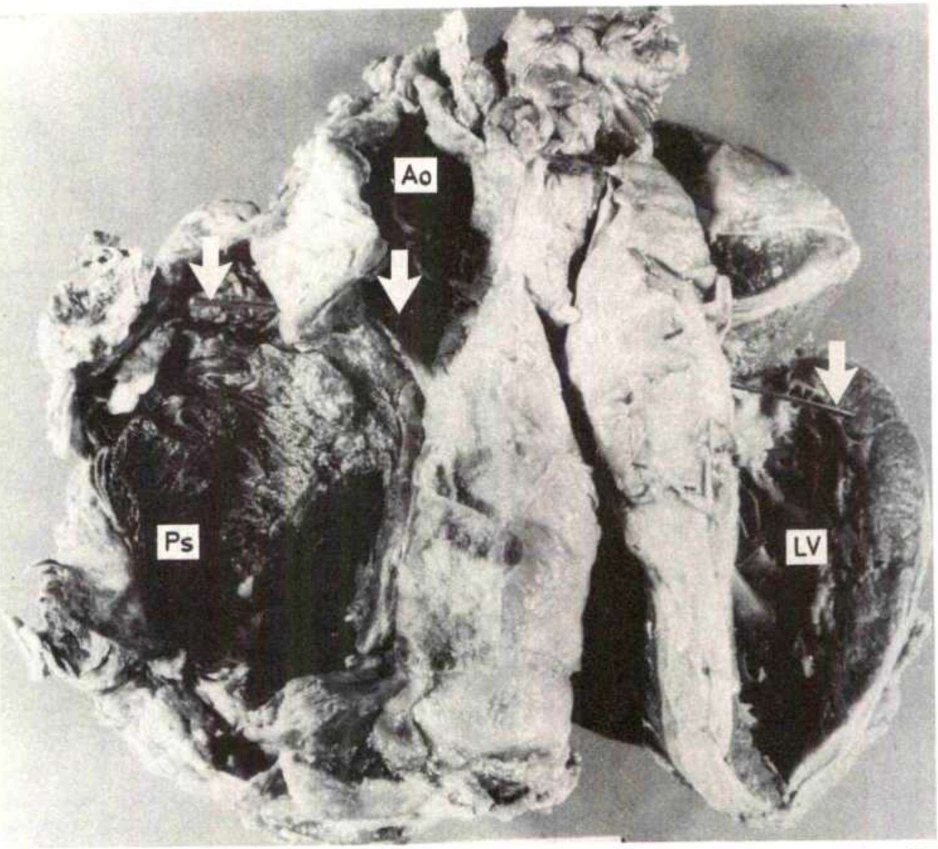

Fig. 2 *Morphological appearance of a large pseudoaneurysm of the aorta (Ps). Note the presence of a probe (arrows) which passes from the left ventricle (LV) through the aortic valve into the ascending aorta (Ao) and through the neck of the false aneurysm into the large cavity of the pseudoaneurysm (Ps), which contains large amounts of clot and fibrinous material.*

showed a flow pattern similar to that obtained within the aorta thus identifying it as the neck of the false aneurysm. The flow profiles in the right heart chambers were dissimilar in contour and direction and showed no communication with the mass.

Cardiac catheterisation showed a tricuspid valve compression deformity with a 5 mm diastolic filling gradient and a small volume fistula into the right atrium from the aorta or sinus of Valsalva. An additional compression deformity was noted affecting the ascending aorta. The angiographic study also indicated dehiscence of the aortic prosthesis with perivalvar leak. Based on these findings, the patient was offered a third operation. Nevertheless, he declined further therapeutic intervention and died several days later.

The postmortem examination confirmed the diagnosis suggested by the Doppler study. The heart was enlarged and weighed 1·25 kg. There was a marginal tear of the aorta at the level of the prosthetic valve which communicated with a massive pseudoaneurysm compressing the entire right side of the heart (Fig. 2). The false aneurysm's greatest diameter was 15·0 cm. The wall of the pseudoaneurysm was composed of fibrin, blood clot, pericardium, and calcified connective tissue with focal areas of lymphocytic infiltrates.

Discussion

Pseudoaneurysms of the ascending aorta are relatively uncommon compared with those evolving from the left ventricle. This is undoubtedly due to the high mortality associated with rupture of the aorta.[2] If the patient survives for several weeks a fibrous walled false aneurysm will form. The amount of time required to convert a pulsating haematoma into a false aneurysm is unknown, although Groves observed such a transformation as early as 23 days.[3] When this occurs in the ascending aorta, blood can be found in the pericardial sac because the parietal pericardium is attached to the ascending aorta just proximal to the origin of the innominate artery. Thus blood can dissect up into the great vessels and cause stenosis of the aortic or pulmonary artery. Blood may also dissect retrogradely and extend into the free wall of the atria, ventricles, or interatrial septum. Thiene *et al* reported 23 of 42 necropsy cases in which aortic rupture showed dissection of blood into the right atrial wall and in eight of these 42 cases had dissected into the interatrial septum.[4] In our patient, the pseudoaneurysm dissected over the anterior aspect of the heart to compress and deform both the right atrium and right ventricle, severely impairing the function of the tricuspid valve. In addition, stenosis of the ascending aorta just proximal to the right innominate artery represents dissection antegradely impinging on the internal diameter of the aorta. In retrospect, the latter should have been a clue to the angiographic diagnosis.

To our knowledge, there has been only one report describing the pulsed Doppler echocardiographic diagnosis of a pseudoaneurysm.[1] Previously, cross sectional echocardiography has been well established as being capable of detecting pseudoaneurysms; but it has not been able to differentiate the entity from a localised haematoma, pericardial cyst, diverticulum, pericardial effusion, or true aneurysm.[5-7] Angiography of the neck of the pseudoaneurysm has been the accepted procedure to confirm the diagnosis. The use of the pulsed Doppler technique has allowed the echocardiographer to determine blood flow characteristics timed with the cardiac cycle throughout the aneurysm, its neck, and the left ventricle. In our case cross sectional echocardiography showed the compression of the right heart. The Doppler technique was then used to trace the flow from the ascending aorta into the pseudoaneurysm. In essence, this accomplished the same feat as angiography but with a greatly reduced risk and cost.

The most dramatic feature in this case is that pulsed Doppler echocardiography was able to demonstrate the neck of the false aneurysm and correctly traced blood flow pattern compatible with aortic flow through the neck into the aneurysm itself. This contrasts with the angiographic diagnosis of a "low flow fistula between the sinus of Valsalva and the right atrium." Pulsed Doppler echocardiography also correctly predicted the lack of communication between the aneurysm and the right atrium or right ventricle. Thus this relatively new technique was instrumental in making the correct diagnosis.

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Echocardiographic features of a mediastinal pancreatic pseudocyst

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SUMMARY Cross sectional echocardiography detected a mediastinal pancreatic pseudocyst which caused extracardiac compression in a 49 year old man. Computed tomography confirmed the presence of a cystic lesion lying behind the heart and extending from the pancreas to above the carina. Surgical decompression resulted in resolution of the clinical and echocardiographic findings.

Causes of posterior mediastinal masses include neurofibroma, neuroblastoma, meningocele, aortic aneurysm, clear water pericardial cysts, and hydatid cysts. The echocardiographic features of cardiac compression due to posterior mediastinal malignant tumours, left atrial wall tumours,[1] and pericardial effusion[2] have been reported.

There have been 30 reported cases of mediastinal extension of a pancreatic pseudocyst[3–10] including one in which the M mode echocardiographic features resembled those of a left atrial myxoma.[11] Nevertheless, the cross sectional echocardiographic features of cardiac compression by a mediastinal pancreatic pseudocyst have not previously been described.

Case report

A 49 year old man with a long history of heavy alcohol consumption had a history of progressive dysphagia, persistent vomiting, dull epigastric pain, and severe weight loss. On examination he was thin and cachectic. Abdominal examination showed no abnormality, and there were no signs of chronic liver disease. His heart rate was 80 beats/minute, blood pressure 120/70 mm Hg, and inspiratory variation within normal limits. The cardiac apex was overactive and displaced to the anterior axillary line in the sixth intercostal space. On auscultation he had a harsh systolic murmur at the left sternal edge which increased with respiration and decreased on standing. His carotid upstroke was normal. Serum amylase activity was 250 IU/L (normal <150 IU/L). Liver function tests were normal, as was the full blood count. Abdominal *x* ray films showed pancreatic calcification and a chest *x*-ray film a small left pleural effusion. The electrocardiogram showed increased QRS amplitude over the precordial leads and lateral T wave inversion. Gastroscopy indicated anterior compression of the oesophagus by a pulsatile mass 5 cm below the level of the cricopharyngeal junction.

Cross sectional echocardiography showed a 10 cm diameter cystic lesion posterior to the heart and outside the pericardium. In the long axis view the cyst compressed the left atrium and left ventricle (Fig. 1), with the left ventricular end diastolic diameter being 2·0 cm (normal >3·5 cm) and the left atrial diameter 1·7 cm (normal >1·9 cm). In the short axis view there was compression of the left and right ventricles and the heart was displaced anteriorly. The cyst extended caudally below the cardiac apex and cranially behind the left atrium. On standing the diameter of the cyst decreased to 8 cm. The heart valves and chambers were otherwise normal.

Computed tomography showed a cystic lesion in the posterior mediastinum extending from the pancreas to above the carina (Fig. 2).

At laparotomy a pancreatic cyst communicating with the mediastinum along the psoas muscle beneath the medial arcuate ligament was found and treated by internal drainage. The amylase content of the fluid was 3500 IU/L.

Postoperatively the patient's clinical state rapidly improved. The systolic murmur disappeared as did the abnormal clinical and electrocardiographic findings. Repeat cross sectional echocardiography two months later showed that the diameter of the cyst had decreased from 10 cm to 3·5 cm. The features of cardiac compression had resolved; notably, the left ventricular end diastolic diameter had increased from

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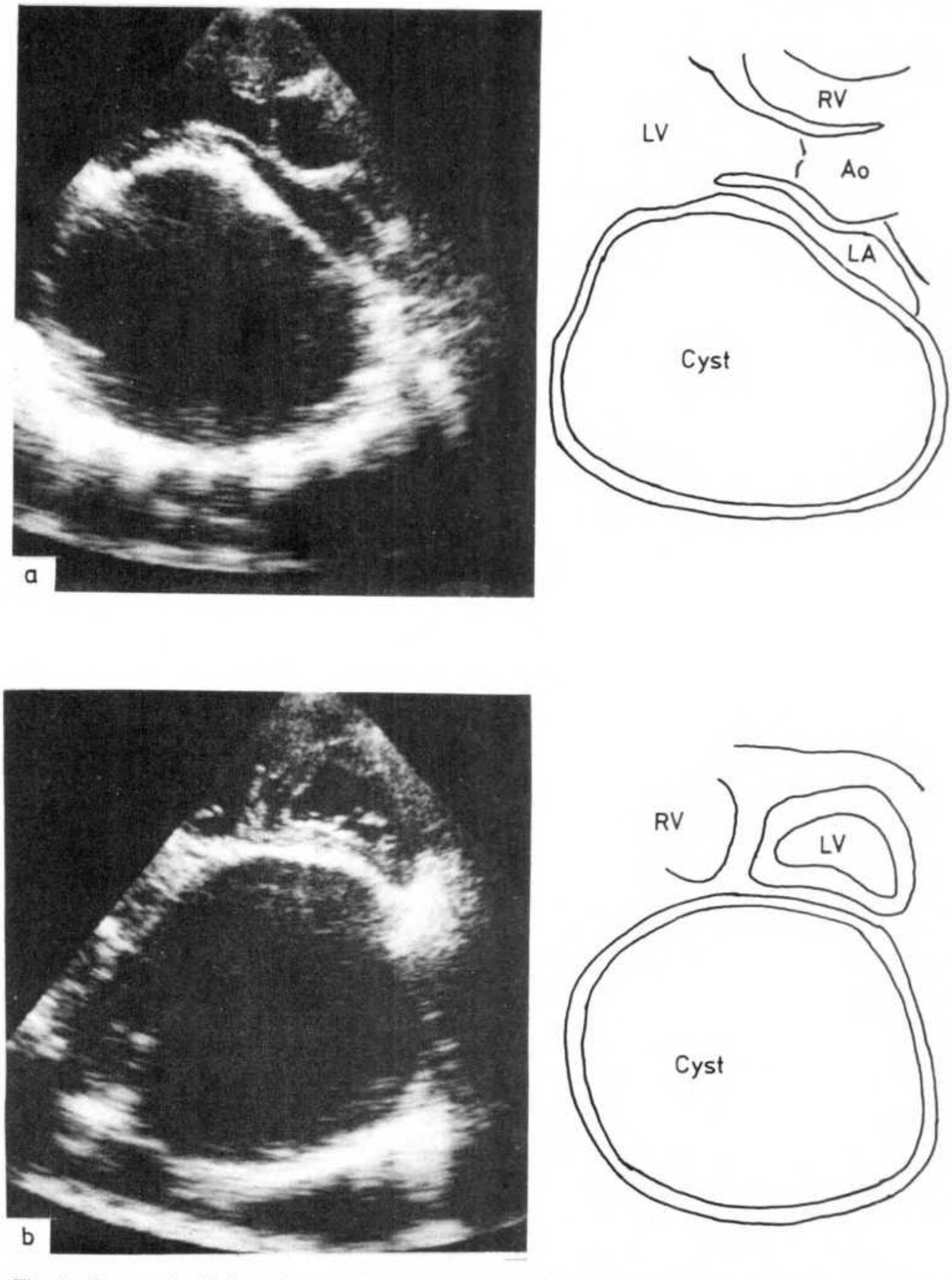

Fig. 1 *Cross sectional echocardiograms in (a) the long and (b) the short axis parasternal views showing a 10 cm diameter cystic lesion posterior to the heart compressing the left atrium (LA) and left ventricle (LV). Ao, aorta; RV, right ventricle.*

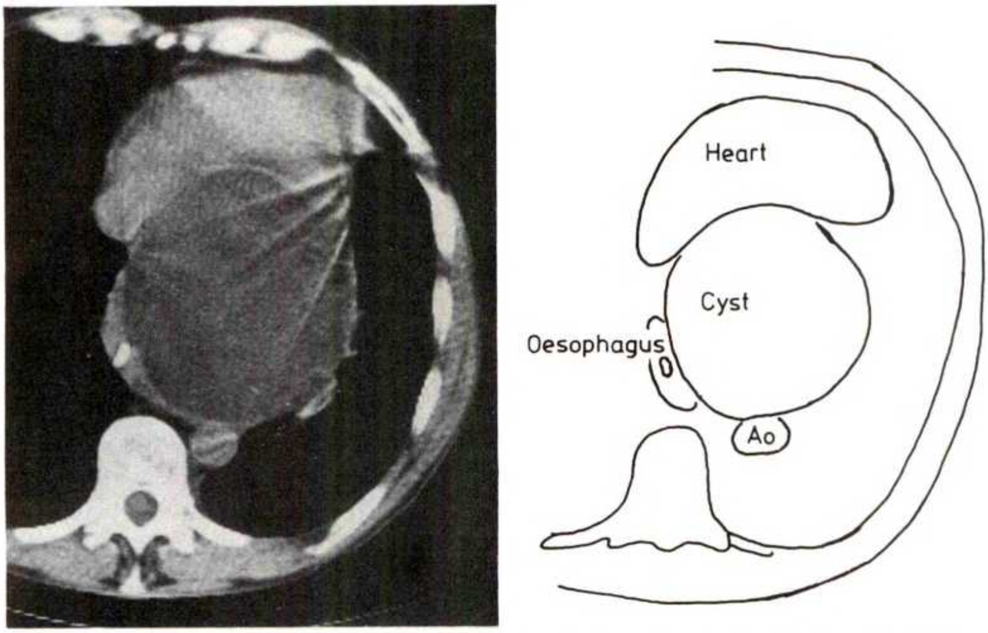

Fig. 2 *Computed tomogram of the thorax showing a large cystic mass posterior to and compressing the heart. The oesophagus is also compressed, and there is a nasogastric tube in position.*

2·0 cm to 3·5 cm and the left atrial diameter from 1·7 cm to 2·7 cm.

Discussion

Weidmann *et al* reported a patient with a mediastinal pancreatic pseudocyst who, before this diagnosis had been made, underwent cardiac catheterisation because of a prominent systolic murmur.[12] Angiography showed pronounced compression of the left atrium and ventricle, and there was a distinct systolic pressure gradient between the inflow and outflow tracts of the right ventricle. These findings correlate closely with those in our case and suggest that the systolic murmur was due to an infundibular pressure gradient in the right ventricle. The pronounced precordial impulse and electrocardiographic features suggesting left ventricular hypertrophy were probably due to anterior displacement of the heart.

The presence of the clinical features of cardiac compression or evidence of a cystic lesion of the posterior mediastinum in patients with chronic alcoholism, pancreatitis, or a pancreatic pseudocyst should raise the possibility of a mediastinal extension of a pseudocyst.

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Br Heart J 1985; 53: 574–6

Complement activation and anaphylactoid response to protamine in a child after cardiopulmonary bypass

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*From the *Department of Cardiac Surgery, Royal Postgraduate Medical School, Hammersmith Hospital; and the †Department of Immunology and ‡Thoracic Unit, Hospital for Sick Children, London*

SUMMARY A 2½ year old boy had a sudden, severe, and unexpected anaphylactoid reaction after an otherwise uncomplicated repair of a partial atrioventricular septal defect. The reaction, comprising haemorrhagic pulmonary oedema and peripheral circulatory collapse, followed neutralisation of heparin by protamine. Measurements of serum complement (C3 and C4) concentrations suggested that a pronounced consumption of complement occurred during the adverse response.

Sudden severe anaphylactoid reactions after an otherwise uncomplicated cardiopulmonary bypass procedure have been reported previously and attributed to an abnormal response to protamine.[1 2] The mechanism of this reaction, which comprises acute haemorrhagic pulmonary oedema with low left atrial pressure, peripheral circulatory collapse, and increased pulmonary vascular resistance, remains elusive. The reaction between heparin and protamine is, however, known to result in the consumption of complement in vitro,[3 4] and recently one of us (SW) found complement activation with C3a release after protamine infusion in patients undergoing coronary artery surgery (unpublished observations).

We recently encountered and successfully treated a severe anaphylactoid reaction after neutralisation of heparin with protamine in a child and obtained evidence of complement activation by the classical pathway.

Case report

A 2½ year old boy was admitted for repair of a partial atrioventricular septal defect. He had no previous history of allergy, blood transfusion, or drug sensitivity. Intracardiac repair was performed uneventfully, and cardiopulmonary bypass was discontinued without difficulty after 39 minutes. His haemodynamic status was stable with a systemic arterial pressure of 100 mm Hg and central venous pressure of 8 mm Hg. The venous cannulas were removed and protamine at a dose of 4·5 mg/kg given slowly over a period of 10 minutes. Five minutes after the infusion had been completed a sudden unexpected reaction occurred. The systemic blood pressure fell to below 30 mm Hg, although the mean left atrial pressure remained at 7 mm Hg. Pulmonary inflation pressure increased with decreasing pulmonary compliance, and there was a palpable rise in pulmonary arterial pressure. Haemorrhagic pulmonary oedema was noted by the anaesthetist when a large quantity of pink frothy secretion was aspirated from the endotracheal tube. Arterial saturation decreased and was followed by ventricular arrhythmia. The pleural cavities were opened to eliminate a local mechanical cause. The lungs were stiff, oedematous, and haemorrhagic.

Treatment was given immediately with intracardiac adrenaline and isoprenaline. A dopamine infusion was started (10 mg/kg/min) and methyl prednisolone given at a dose of 30 mg/kg. Sodium bicarbonate was required to correct metabolic acidosis, and plasma was infused to maintain right and left atrial pressures at satisfactory levels (left arterial pressure 7–10 mm Hg). After a short period of cardiac massage the systemic pressure slowly rose. Subsequently, a period of systemic hypertension occurred, and frusemide 10 mg (1 mg/kg) was given. During the period of resuscitation blood samples were taken to rule out a transfusion reaction to donor blood and for estimating concentrations of complement.

With this treatment the haemodynamics stabilised, and the chest was closed. A chest radiograph after return to the intensive care unit showed bilateral pulmonary oedema. The pulmonary oedema resolved completely during the next 24 hours, although the

Requests for reprints to Mr J Stark, Thoracic Unit, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

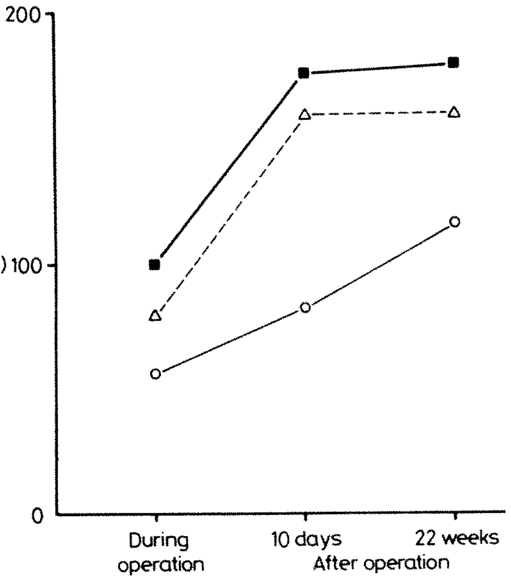

Figure *Concentrations (percentage of standard) of the complement components C3 (■) and C4 (△) and total haemolytic complement (○) (percentage of normal) in the patient at three sampling times.*

boy required intermittent positive pressure ventilation for 48 hours. His subsequent postoperative course was uneventful, and he was discharged from hospital after 10 days.

Since a satisfactory preoperative blood sample was not available for baseline complement assays further samples were taken at 10 days and 22 weeks postoperatively. The Figure shows the C3 and C4 concentrations measured by single radial diffusion and the results of the total haemolytic complement assays. In contrast to the changes in the concentrations of the complement component the serum albumin concentrations during and after operation were exactly the same (55 g/l). Studies of three similar patients undergoing surgery who received protamine without incident had essentially stable C3 and C4 concentrations before and after infusion (coefficient of variation ≤13% and 8% respectively).

Discussion

In this case study late postoperative C3 and C4 concentrations were almost identical to the 10 day samples and were assumed to reflect the patient's values for these acute phase proteins. In contrast, the sample taken during operation after the onset of pulmonary oedema and peripheral circulatory collapse showed a pronounced reduction in C3, C4, and total haemolytic complement suggesting that complement had been activated by the classical pathway.

Complement activation with release of the anaphylatoxins C3a and C5a is known to occur via the alternative pathway during cardiopulmonary bypass.[5] C4 is not consumed in this process, and complement activation after protamine infusion occurs by a separate mechanism. This polycationic polypeptide produces cardiovascular side effects, characterised by Jastrebski *et al* in 1974, as a transient fall in systemic arterial pressure with a more prolonged rise in pulmonary arterial pressure.[6] This is accompanied by a pronounced fall in arterial oxygen tension owing to a reduction in mixed venous oxygen tension which follows a fall in cardiac output. Left atrial pressure remains low implying an increase in pulmonary vascular resistance.[7] The mechanism of these effects is still not clearly defined, but because of them protamine is infused slowly. The anaphylatoxins C3a and C5a have potent vasoactive properties. They increase vascular permeability, cause histamine release from mast cells, constrict smooth muscle, and may well account for the anaphylactoid reactions experienced by some patients.[8] Polymorphonuclear leucocytes and monocytes have membrane binding sites for C5a.[9] C5a release results in altered mobility of these cells with sequestration in the pulmonary capillaries, a process associated with capillary endothelial damage and pulmonary oedema.[10 11]

Previously, both anaphylactic[12] and anaphylactoid responses to protamine infusion have been reported. Nordstrom *et al* described a case similar to our own in a 6 year old girl.[1] Olinger *et al* described four patients with non-cardiogenic pulmonary oedema and peripheral vascular collapse from two separate cardiac units between 1969 and 1978.[2] Of these, two patients died of low cardiac output and hypoxia while two survived after treatment with intravenous colloid infusion, methylprednisolone, catecholamines, and antihistamines. There were, however, notable differences in the character of these reactions between the patients, who cannot be assumed to be a homogeneous group. A variety of mechanisms may result in the syndrome of pulmonary hypertension, peripheral circulatory collapse, and increased capillary permeability. Among these are blood and drug reactions, endotoxic shock, allergic anaphylaxis, and nonimmune reactions mediated by complement and histamine.[13] Our patient survived but required prompt and aggressive resuscitation directed towards a complement mediated anaphylactoid shock.

We thank Mr N Seymour for the assays of complement proteins.

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Notices

European coronary angioplasty workshop

A meeting on coronary angioplasty is to be held from 10 to 12 July 1985 at The London Hospital. Further information may be obtained from: PTCA Workshop, c/o Cardiac Department, The London Hospital, Whitechapel, London E1 1BB.

Geriatric cardiology

The 2nd International Conference on Physical Activity, Aging, and Sports will be held at West Point, New York, from 8 to 12 July 1985. Further information may be obtained from PAAS—'85, Center for the Study of Aging, 706 Madison Avenue, Albany, New York 12208, USA.

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts will be 2 January 1986.

Br Heart J 1985; 53: 577–84

Correspondence

Left ventricular function in coronary artery disease

Sir,
I write concerning the article by Lahiri *et al* on the "Assessment of left ventricular function in coronary artery disease with the nuclear probe during intervention studies" (1984; **52:** 422–30). The data on ejection fraction changes during effort is interesting. There is, however, a problem with the method of determining filling and ejection rates. Ejection and filling rates are calculated by the probe according to the formula:

$$\frac{CT3 - CT2}{T3 - T2} \times \frac{1}{Cn}$$

where CT3 is the counts at cursor position T3, CT2 counts at cursor T2 (T3 and T2 represent the time positions of the T3 and T2 cursors), and Cn the normalisation counts. Normalisation counts equal CT1 minus BKG when T1 is not equal to 0, and when T1 is equal to 0 Cn equal to BKG. When T1 is positioned at the midpoint between T2 and T3, ejection rate will be normalised to average counts. When T1 is positioned at the end diastolic counts filling rate will be normalised to end diastolic volume. Both exercise and the administration of nitrates may, however, be expected to change ventricular volume. If ventricular volume changes then the normalisation counts will change producing apparent changes in filling or ejection rate not reflecting true changes in these variables. To deal with this problem the T1 cursor should be positioned at 0 and normalisation will then be to background counts. Under these circumstances changes in filling or ejection rate may be followed independently of changes in ventricular volume. As things stand it may be thought that no reliance can be placed on quoted changes in filling or ejection rate.

David Robson,
Greenwich District Hospital,
London SE10 9HE.

This letter was shown to the authors, who reply as follows:

Sir,
We have carefully considered Dr Robson's comments about our paper (1984; **52:** 422–30). In reply to his comments we would like to establish certain facts.

Firstly, the measurement of slopes from the left ventricular time-activity curves by the computer of the nuclear stethoscope is based on relative rather than absolute left ventricular volumes. The methods used for calculating peak filling rate are based on those described by previous authors—namely, Bonow *et al*,[1] Reduto *et al*,[2] and Mancini *et al*,[3] and these have been quoted in the text.

Secondly, in patients with obstructive coronary artery disease, during exercise induced myocardial ischaemia, the following changes occur: changes in left ventricular volume, increases in left ventricular end diastolic pressure, left ventricular wall tension, left atrial pressure, and increased cardiopulmonary blood volume and increased pulmonary wedge pressure.[4]

Thus exercise induced ischaemia would affect both left ventricular end diastolic volume and background counts (which represents cardiopulmonary blood volume). Nitrates therefore would have a reverse effect on both these variables. Thus, in our opinion, the correction or normalisation of the slope to end diastolic volume or background would have the same errors as indicated by Dr Robson. We have, in fact, applied both of these corrections to the peak filling rate in previous experiments and found that the direction of changes is similar. We do agree, however, that during intervention studies using the nuclear stethoscope or the gammacamera the values of the rates of filling and emptying are relative unless one is able to perform attenuation correction and convert the relative data into absolute volumes.

Thus it follows that "normalisation to background counts allow changes in filling or ejection rate to be followed independently of changes in ventricular volume" is manifestly incorrect since all the volume variables change during interventions with exercise or with nitrates in patients with obstructive coronary artery disease.

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Middlesex HA1 3UJ.

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Analysis of circadian blood pressure rhythms

Sir,

We read with interest the observation by Davies *et al* (1984; **52:** 93–8) on the circadian rhythm of blood pressure. The authors state that Millar-Craig *et al* reported a second peak of blood pressure in the early evening.[1] We consider that this is not a correct citation, as Millar-Craig *et al* reported that "... blood pressure fell progressively during the day and rose in the early hours of the morning."

Davies *et al* mention the difficulties in quantifying variations in the blood pressure. Some of the basic work on rhythmic blood pressure changes (summarised in[2]) deals with the problems of recording, reproducibility, and analysis of blood pressure patterns. Using cosinor analysis, first introduced by Halberg *et al*[3] might improve the accuracy of analysis. It provides an exact calculation of rhythm variables such as mesor, amplitude, and acrophase of circadian rhythmic changes.[4–6] It would be interesting to evaluate the carefully documented data of Davies *et al* by cosinor analysis. We wonder whether this method of analysis would confirm the reported two hour difference between the nadir of the paced group and the control group.

The authors also point out that the amplitude of the cirdacian pattern was lower in the paced than in the hypertensive group. Judging from the data in Fig. 1 of their article this seems not unlikely. Quantitative evaluation of the amplitudes, however, is not reported but might be done by cosinor analysis. Furthermore, cosinor analysis might allow a better comparison of circadian heart rate and blood pressure variations.

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Ekkehard Haen,†
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This letter was shown to the authors, who reply as follows:

Sir,

We thank Drs Gerbes *et al* for their interest in our paper on circadian rhythms of blood pressure in paced patients. They correctly cite our original description of the broad 24 hour pattern of blood pressure[1]; however, most of our data on closer inspection showed a subsidiary late afternoon rise of lower amplitude than that seen after waking. This is visible in Figs. 1 and 3 of the original publication.[1]

The problems inherent in describing ambulatory intra-arterial blood pressure patterns have been recognised by several groups of workers. We find it difficult to accept that Halberg's cosinor analysis would be able to provide sufficient accuracy in this case. As we understand it, the technique consists of fitting a single 24 hour cosine curve to the data using the method of least squares. Variables such as the amplitude, mesor (average value), and acrophase (timing of the peak relative to an arbitrary time origin) are then measured from the fitted curve. The pattern of blood pressure is not symmetrical within a 24 hour cycle; for example, a single cosine function would be a very poor fit to the systolic data in Fig. 1 of our paper. This observation appears to be confirmed by the work of Murnaghan *et al* in their study of blood pressure in pregnancy.[2] The single cosinor technique failed to give sufficient resolution to describe other than gross features of the blood pressure patterns. Walsh and Goldberg also found that significant components were present at higher frequencies.[3] Detailed studies by Sayers[4] indicate the presence of several concurrent patterns, posing severe problems in any detailed statistical analysis across patients. More recently, the same group has suggested a set of procedures for pattern analysis of these records, relying more on measurements from each record than on a priori models.[5] These procedures are at present being applied to blood pressure data from a variety of sources.

In active untreated subjects the timing of the acrophase must be heavily dependent on the time of waking since this is the event which has the greatest effect on blood pressure. This would tend to place the acrophase at approximately 14 hours before waking—that is, at 1800 or so, and this has been the finding of several workers.[3 6] It is hard to see how this would provide any illumination of our observed shifts in the nadir of blood pressure at around 0100–0300. For critical studies we now compile our data relative to waking time as well as to absolute clock time.

We are therefore unconvinced that cosinor analysis would clarify our observations of ambulatory intra-arterial blood pressure unless applied in a complex form taking account of many pattern features and frequencies, in which case conventional Fourier analysis seems to offer more possibilities.

E B Raftery,
P M M Cashman,
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Delayed recovery of left ventricular function after antithyroid treatment

Sir,
Forfar *et al* (1984; **52:** 215–22) suggest that in hyperthyroidism left ventricular function is reversibly depressed. Their conclusions are based on haemodynamic measurements performed on 15 hyperthyroid subjects before and during isometric exercise, and those measurements were repeated after the subjects had been rendered euthyroid. The authors stress that hyperthyroidism involves changes intrinsic not only to the heart itself but also to the peripheral circulation. They assume, however, that the performance of a standardised isometric exercise task produced the same changes in the peripheral circulation in both hyperthyroid and euthyroid states and, therefore, that exercise caused the same changes in cardiac loading before and after the subjects had been treated for their thyrotoxicosis. Nevertheless, as shown in the Table below, using data taken from their own paper it may be calculated that isometric exercise actually caused directionally opposite changes in peripheral vascular resistance during the thyrotoxic and euthyroid states. Peripheral vascular resistance is a major determinant of the impedance offered to the outflow of blood from the left ventricle. In the study of Forfar *et al* the thyrotoxic heart, faced with an increased peripheral resistance during isometric exercise, did not function as well as it did at rest. In contrast, the euthyroid heart experienced a large reduction in calculated peripheral vascular resistance during isometric exercise and showed no deterioration in function.

Thus it would appear that peripheral resistance is an important determinant of basal and exercise induced left ventricular function in thyrotoxicosis, and the results obtained by Forfar *et al* do not establish the presence of an intrinsic myocardial abnormality in the thyrotoxic state.

B Northover,
B P O'Malley,
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Leicester,
LE1 5WW.

This letter was shown to the authors, who reply as follows:

Sir,

Northover *et al* do not indicate how they have determined systolic and diastolic volumes from the left ventricular diameters given in our paper. Their derived stroke volume in the euthyroid state at rest, for example (19·4 ml) at a measured heart rate of 82 beats/min, gives a cardiac output of 1·6 l approximately, an output so low that it is biological nonsense in the context of our study. Similarly, their derived figure for cardiac output in the hyperthyroid group at rest (2·8 l/min) is over four times less than that of Merillon *et al*[1] based on direct invasive measurements (13·1 l/min). We doubt whether the errors and assumptions involved in the derivation of left ventricular volumes by single element echocardiography[2] justify their usage in a study of this type, let alone as a basis for calculating peripheral vascular resistance.

The conclusion of our study that left ventricular function is depressed in hyperthyroidism is not dependent on isometric exercise causing the same changes in peripheral-vascular resistance in the hyperthyroid and euthyroid state. Indeed, this is most unlikely in view of the profound reduction in peripheral vascular resistance in hyperthyroidism. During isometric exercise vascular resistance will certainly be lower in hyperthyroidism. Crude derivation of vascular resistance from our study (using the formula of Feigenbaum *et al* for ventricular volumes[3]) supports this contention. Despite this reduction in peripheral vascular resistance, the pre-ejection period during isometric exercise was significantly longer in the hyperthyroid (144(4) ms) than in the euthyroid (135(4) ms) state. This significant prolongation in exercise pre-ejection period in hyperthyroidism was maintained after autonomic blockade.

The results of our study suggest reversible abnormalities in left ventricular contractile responses to exercise in hyperthyroidism that may persist for some weeks after the restoration of a biochemical euthyroid state.

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Table *Effects of antithyroid treatment on left ventricular function*

Measurement	*Source*	*Hyperthyroid*		*Euthyroid*	
		Resting	*Exercising*	*Resting*	*Exercising*
Systolic arterial pressure (mm Hg)	Forfar *et al*	126	151	119	144
Heart rate (beats/min)	Forfar *et al*	99	108	82	93
Ventricular diastolic diameter (cm)	Forfar *et al*	4·2	4·3	4·0	4·1
Ventricular diastolic volume (ml)*	Calculated	38·8	41·6	33·5	36·1
Ventricular systolic diameter (cm)	Forfar *et al*	2·7	3·2	3·0	2·9
Ventricular systolic volume (ml)*	Calculated	10·3	17·2	14·1	12·8
Ventricular stroke volume (ml)*	Calculated	28·5	24·4	19·4	23·3
Cardiac output (l/min)	Calculated	2·84	2·64	1·59	2·17
Peripheral vascular resistance (mm Hg min/l^{-1})	Calculated	44·3	57·2	74·8	66·4

*In the calculations of ventricular volume the ventricle was assumed to be spherical.

Continuous recording of pulmonary artery pressure

Sir,
The statement by Ikram and his coworkers in their paper on continuous pulmonary artery pressure recording (1984; **51**: 421–6) that: "The total (measurement) system has a frequency response linear to 8 Hz allowing accurate pressure recording over the full range of heart rates" should not pass unchallenged.

Ikram suggests that, although the catheter-transducer pressure measurement system is underdamped with its resonant peak at 16 Hz, these characteristics are compensated by the limited frequency response of the Medilog tape recorder and playback system. The problems of low frequency catheter resonance have been discussed in detail by McDonald[1] and by Gabe.[2] Gabe pointed out that if the catheter-transducer damping factor is around 0·2, which my measurements on a portable transducer perfusion unit and No 5 Goodale Lubin catheter confirm, the highest frequency component which can be measured without distortion of the signal is about 20% that of the resonant frequency; in this case up to 4 Hz. Ikram presents a Millar catheter record of pulmonary artery pressure, a simultaneous record obtained by the transducer catheter system, which shows resonance, and a "clean" version of the record after replay through the recording system (Figs. 3 and 4). Although the waveforms are said to match each other, the pulse pressure is about 15% greater in the underdamped system compared with the Millar catheter, and after replay the pulse pressure is apparently attenuated by nearly 50%. Furthermore, the gross distortion of the replayed "clean" waveform in the region of the dichrotic notch leaves one with little confidence that the systolic and diastolic pressures will be recorded accurately.

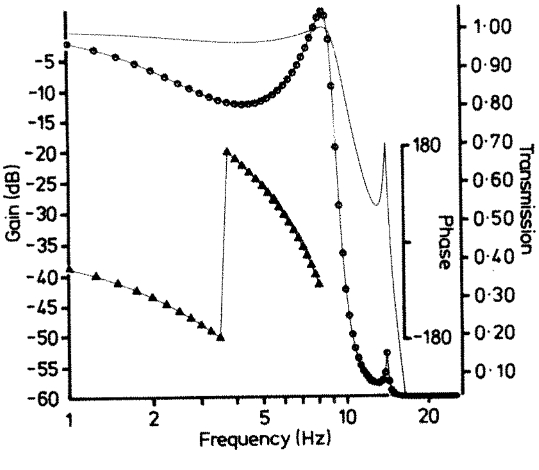

Fig. 1 *Plot of gain in decibels (unbroken line), transmission (○) and phase (▲) as a function of log 10 (frequency) for the transducer-catheter system and the Medilog recorder. These curves were obtained from the measured frequency response of the recorder-playback system (filter 4, gain 5) and the calculated characteristics of the catheter-transducer using a "pop" test.*

Ikram shows the frequency response of the entire recording system (Fig. 2 in his paper). Using the measured frequency response of the Medilog recorder and replay unit (AM4 recorder amplifier and PB2 replay unit with PM3 amplifiers) and by treating the catheter and transducer as a classical second order system with its variables determined by a "pop" test,[1] the frequency response of the entire system may be approximated and is shown in Fig. 1. The agreement with Ikram's results is reasonable, although the −2 dB (21%) attenuation at 2·5 Hz shown in his paper cannot be reproduced precisely. When this curve is plotted as transmission rather than gain in decibels it is clear that the response of the system is far from flat within the physiologically significant range of frequencies.

This passband characteristic arises from three effects. The signal is attenuated by a simple presettable filter in the Medilog replay system, and attenuation will occur throughout the physiologically significant range of frequencies. This attenuation is, however, offset with increasing frequency because the effect of the resonant peak of the catheter becomes more significant. Also, the demodulator in the replay unit uses a very sharp filter with a corner frequency set at 8 Hz. Although this filter has a nominally flat passband, there is a slight increase in transmission at around 8 Hz (this overshoot in transmission is adjustable using a preset control in the replay unit) so further offsetting the attenuation of the simple presettable filter.

Such a system does not damp catheter resonance correctly. It relies on the slightly non-ideal characteristics of the replay unit demodulating filter which varies between individual units. It also relies on precise catheter resonance characteristics. McDonald[1] and Gabe[2] emphasise that the frequency response of a catheter transducer system near its resonance depends on the exact resonant frequency and the damping. The frequency response of the catheter, and hence the response shown in Fig. 1, may be dramatically modified by the formation of small bubbles within the catheter, which lower the resonant frequency and

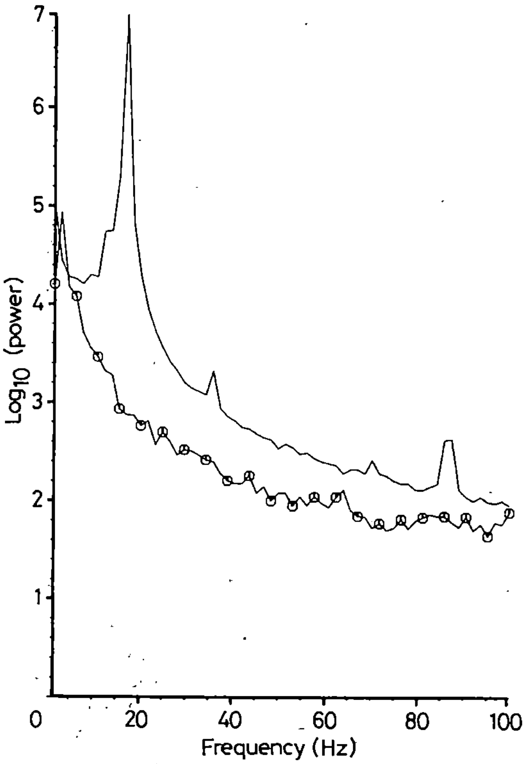

Fig. 2 *Mean power spectral density of replayed signals from the Medilog recorder after recording a 16 Hz tone (unbroken line) and 60 Hz (symbols). The replayed signal (filter 0, gain 5) was digitised at 12 kHz with the 3 dB point of the antialiasing filter set at 6 kHz. The signal was recorded in blocks of 256 points, tapered with a half cosine bell, and the power spectrum obtained using the FFT algorithm. The curves are the means of 43 records.*

increase the damping, and also by the formation of very small clots at its tip, which increase the damping. The shape of a recorded signal depends not only on the relative amplitude of the various Fourier components but also on their respective phases. An ideal system, such as an optimally damped resonant system, has a phase response which increases linearly with frequency and corresponds to delay in the signal without modification of its shape. The calculated phase response of the catheter, recorder, and replay system is shown in Fig. 1. It is decidedly non-linear in the passband, resulting in severe signal distortion.

The expected error in pulse pressure using this system can be estimated by convolving a known simulated waveform (derived from Millar catheter data) and the measurement system impulse response. This calculation shows that there can be up to ±15% error in measured pulse pressure which will depend on the heart rate, replay unit filter setting, and the shape of the measured waveform. In practice, the overall behaviour of the recording system is likely to be worse than is suggested in Fig. 1 because of intrinsic recorder noise. Sayers *et al* have shown that systemic arterial pressure waveforms, measured with a portable transducer perfusion unit and a Medilog recorder, are degraded so that they cannot be distinguished from noise above 6 Hz.[3]

Finally, Ikram's frequency response plot shows two resonant peaks, one at 16 Hz and the other at about 60 Hz, which is attributed to the NIH catheter. The 60 Hz peak is very heavily attenuated by the applied filter and the resonant mode at 16 Hz to approximately −90 dB. The amplitude of this peak would therefore be expected to be in the region of 5000. There is, however, no possibility of this peak being a genuine part of the measured signal because the Medilog recorder uses pulse width modulation to record a DC biased signal and has a carrier frequency of 40 Hz.[4] A 16 Hz sine wave was recorded on a Medilog recorder and the smoothed power spectrum of the replayed signal estimated to see if the peak at 60 Hz represents the 16 Hz peak reflected in the first modulation sideband of the signal. In addition, a 60 Hz sine wave was recorded and the smoothed power spectrum of the replayed signal was obtained. The results of these experiments are shown in Fig. 2. The 16 Hz tone is replayed faithfully, but there is no evidence of a 60 Hz component representing a modulation sideband. The 60 Hz tone is undetectable on replay.

The data presented by Ikram and his coworkers, and that obtained by myself, suggest that the combination of a portable transducer perfusion unit, a No 5 Goodale Lubin catheter, and a Medilog recorder in its DC mode has a frequency response which is inadequate for precise dynamic measurements of pulmonary artery pressure but is adequate for recording slowly moving fluctuations in mean pressure.

R C Saumarez,
Lung Function Unit,
Brompton Hospital,
London SW3 6HP.

References

1 McDonald DA. The design of manometers. In: *Blood flow in arteries.* 2nd ed. London: Edward Arnold, 1974: 174–208.

2 Gabe IT. Pressure measurement in experimental physiology. In: Bergel DH, ed. *Cardiovascular fluid dynamics,* vol 1. London and New York: Academic Press, 1972: 11–50.

3 Sayers BMcA, Ellis NE, Green H. Minimum and maximum requirements for physiological measurement; intra

arterial blood pressure. EEC contract report 297-76-12 ECI. Section 5. 1978.
4 *Medilog MR-10 recorder service manual.* Oxford: Oxford Medical Systems.

This letter was shown to the authors, who reply as follows:

Sir,

We would like to respond to Dr Saumarez's criticism of our technique for recording ambulatory pulmonary arterial pressure in man.

Our first comment is that he has assumed that Fig. 3 and Fig. 4 (p 424) come from the same patient. This is not the case and nowhere is this stated or implied in our paper. The purpose of Fig. 3 was to depict a comparison of waveforms from a high fidelity transducer tipped Millar catheter and a simultaneously recorded pressure using the Akers strain gauge with the fluid filled catheters used in our ambulatory system. Figure 4 is an example of the waveform produced by the Medilog playback unit, but they are from different patients. Hence his conclusions on waveform distortion based on that assumption are probably incorrect.

His comments on the frequency response of the total system are based on actual measurements of only some of the components, while the response of others has been calculated from published specifications. We, on the other hand, have tested the response of the entire system with a swept frequency generator and pressure chamber. This has produced the results depicted in our Fig. 2 (p 423).

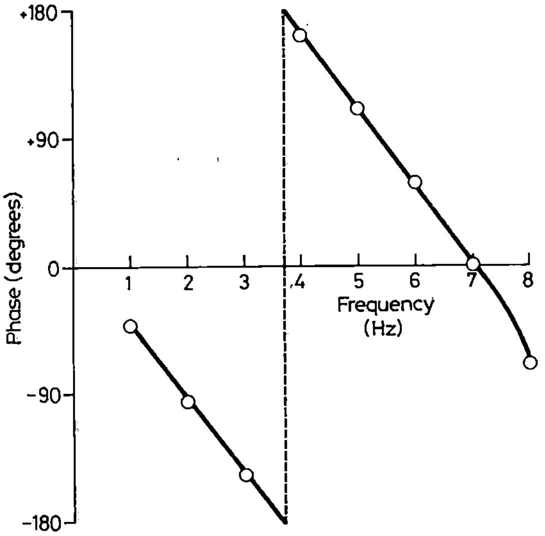

Fig. 1 *Phase response in relation to frequency response.*

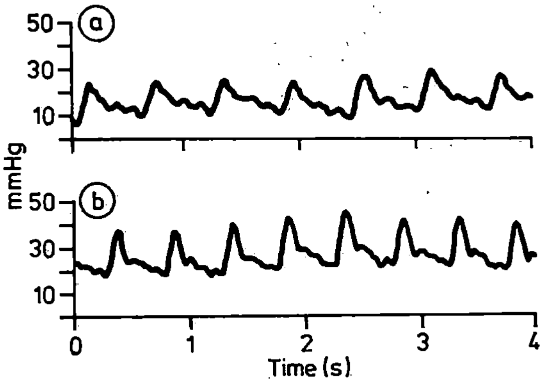

Fig. 2 *Pulmonary arterial pressure (mm Hg) (a) at rest and (b) at submaximal exercise.*

His comments on the probable effects of microbubbles and clots on resonance and frequency response would apply to any catheter manometer system. In practice we have not found this to be a problem once a suitable catheter, heparin dose, and pump speed were perfected.

As regards the phase linearity, Saumarez's Fig. 2 plots phase response against the logarithm of the frequency. If phase is replotted against a linear frequency scale then it is evident that phase response is linear to above 7 Hz (Fig. 1).

Milnor states that 95% of the energy in the pulmonary arterial waveform lies within the first six harmonics.[1] This would suggest that our system is adequate to record the waveform at rest and moderate exercise. Figure 2 shows the waveform obtained in a patient at rest and during submaximal levels of exercise. This clearly shows systolic and diastolic peaks as well as the dicrotic notch and "a" wave at a heart rate of 120 beats/min. Despite theoretical problems, the system in practice does better than "follow slow oscillations around the mean" as Saumarez says. His reference to Sayers *et al's* comment[2] that systemic arterial pressure is unrecordable over 6 Hz using the Medilog system is inappropriate in the context of the pulmonary artery. In this vessel the mean pressure is low and the pulse pressure is a greater proportion of the mean pressure—that is the harmonics have a higher power content.

For these reasons we believe that our method is capable of recording systolic and diastolic pressures with reasonable accuracy but, as is readily acknowledged in our paper, it is incapable of high fidelity waveform reproduction.

The ultimate reason for developing the technique is to provide hitherto unobtainable physiological data on the pulmonary circulation. Our studies on patients suggest that this is possible despite the obvious compromises inherent in a fluid filled low fidelity system. But until the inevitable development of better methods, it remains a practical method currently available for this purpose.

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E J Hamilton,
M G Nicholls,
Department of Cardiology,
The Princess Margaret Hospital,
Christchurch,
New Zealand.

References

1 Milnor WR. Pulmonary haemodynamics. In: Bergel DH, ed. *Cardiovascular fluid dynamics*, vol. 2. London and New York: Academic Press, 1972:299–340.
2 Sayers BMcA, Ellis NE, Green H. Minimum and maximum requirements for physiological measurement; intra arterial blood pressure. EEC contract report 297-76-12 ECI. Section 5. 1978.

This letter was shown to Dr Saumarez, who replies as follows:

Sir,

Ikram *et al* (p 583) have replotted the phase response in Fig. 1 of my first letter (p 581), and the replotted data purport to show that the phase response of their measurement system is linear over its operating range. They have not plotted the data correctly and the conclusion they have drawn is false. Figure 1 in my letter is a Bode plot. The characteristic of an ideal system when its phase is plotted in this way is that there is a constant phase increment for a constant frequency increment rather than that the plot is a straight line. Admittedly, this is hard to see when the plot is reduced in scale. I have replotted the phase shift of the system as difference from the ideal linear phase change over the range 1–8 Hz (Figure), and it is quite clear that the phase response is non-linear. There is approximately 25° phase lead at 5 Hz. This has a profound effect on signal distortion. At a heart rate of 100 beats/minute, the second and third harmonics of the pressure waveform will contribute about 30–40% of their maximum amplitudes to the measured instantaneous pressure signal at a time when they have no contribution to the undistorted waveform. It is this effect, as well as amplitude distortion, which renders the catheter/transducer/Medilog system an unsatisfactory instrument for measuring any dynamic feature of the pulmonary artery pressure waveform.

R C Saumarez,
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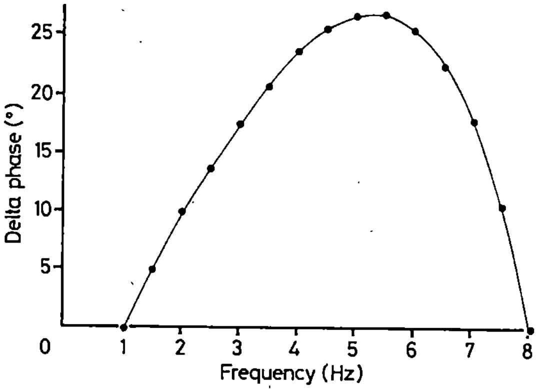
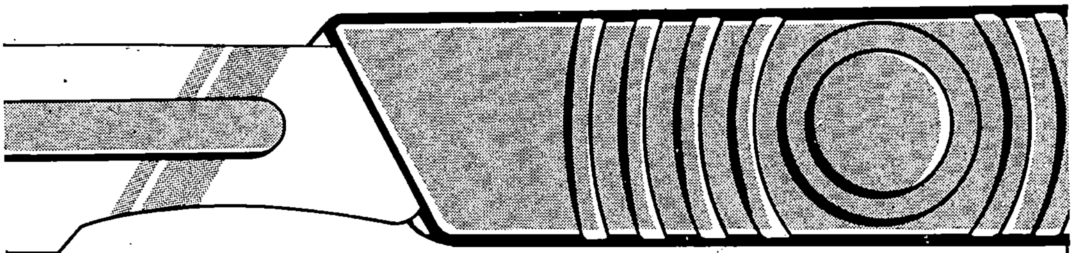


Figure *Difference between the phase response of the catheter/transducer/Medilog system and the ideal linear phase response over the range 1–8 Hz plotted as a function of frequency.*



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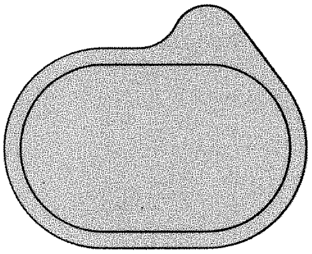

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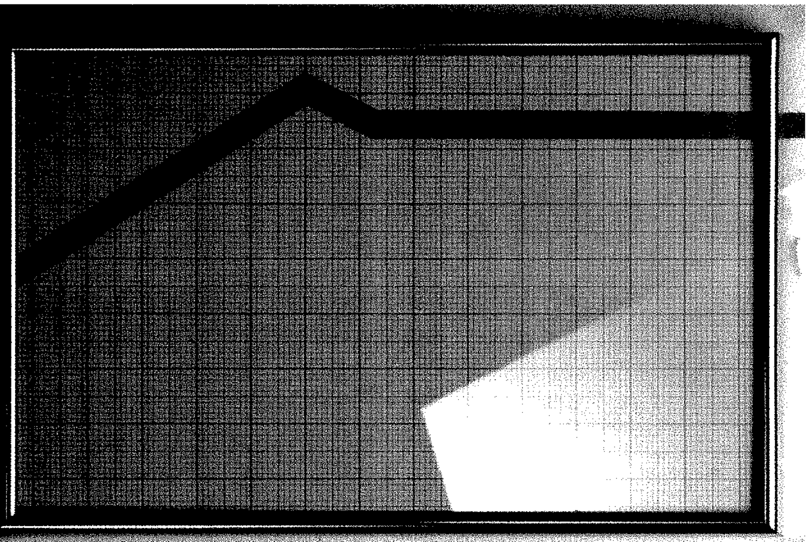

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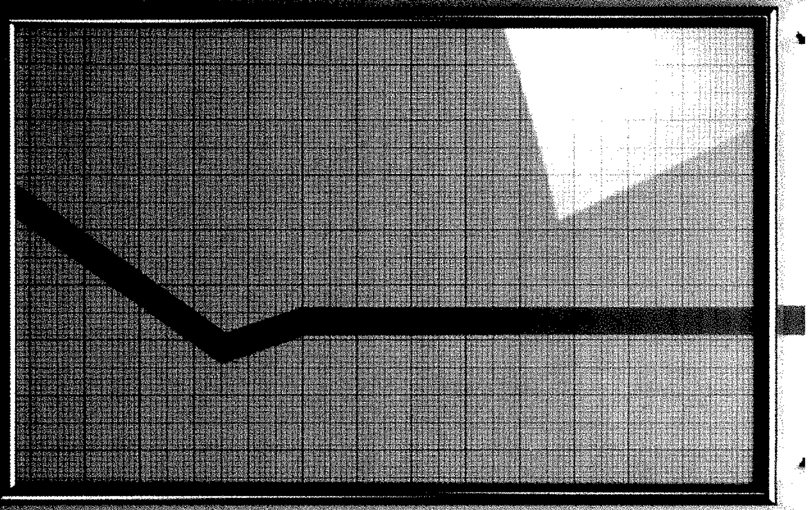

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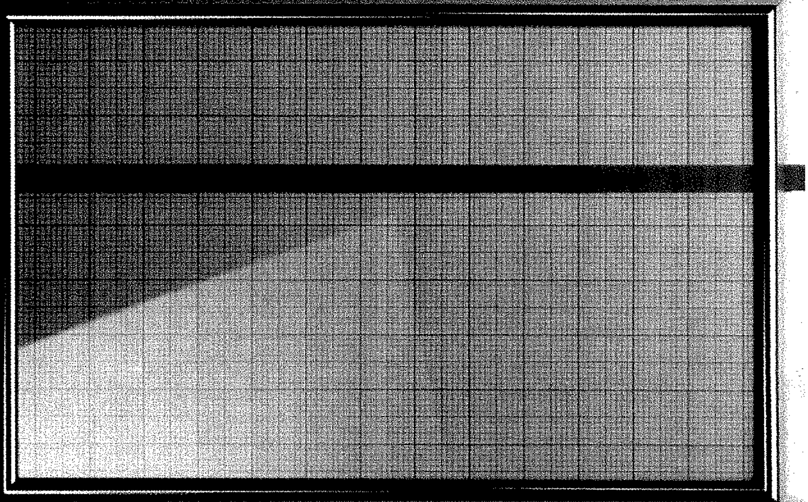

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Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of 'Innovace' and their renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Some hypertensive patients, with no apparent pre-existing renal disease, have developed minor and usually transient increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required.
Renovascular hypertension: 'Innovace' can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 'Innovace' is dialysable.
Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

DRUG INTERACTIONS
Increased antihypertensive effect when combined with methyldopa, ß-blockers, and diuretics. Add ganglionic- or adrenergic-blocking drugs with caution. Plasma potassium usually remains within normal limits. If 'Innovace' is given with a diuretic, diuretic-induced hypokalaemia may be ameliorated. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics should be given with caution, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. Lithium levels may be increased.

SIDE EFFECTS
Generally well tolerated. Most side effects mild and transient, and have not required discontinuation of therapy. Most frequently: dizziness, headache, fatigue, asthenia. Others include hypotension, orthostatic hypotension, nausea, diarrhoea, muscle cramps, rash, cough, dysgeusia, and angioneurotic oedema. With minor and transient rises in blood urea or creatinine, dosage reduction and discontinuation of 'Innovace' and/or the diuretic may be required.

BASIC NHS COST
Tablets 20 mg: calendar packs of 28 tablets, £13.10; bottles of 50 tablets, £23.40. Tablets 10 mg: calendar packs of 28 tablets, £10.40; bottles of 50 tablets, £18.57. Tablets 5 mg: bottles of 50 tablets, £12.30.

PRODUCT LICENCE NUMBERS
Tablets, 5 mg, 0025/0194, Tablets, 10 mg, 0025/0195, Tablets, 20 mg, 0025/0196.

MSD
MERCK SHARP & DOHME

Issued February 1985 TM denotes trademark

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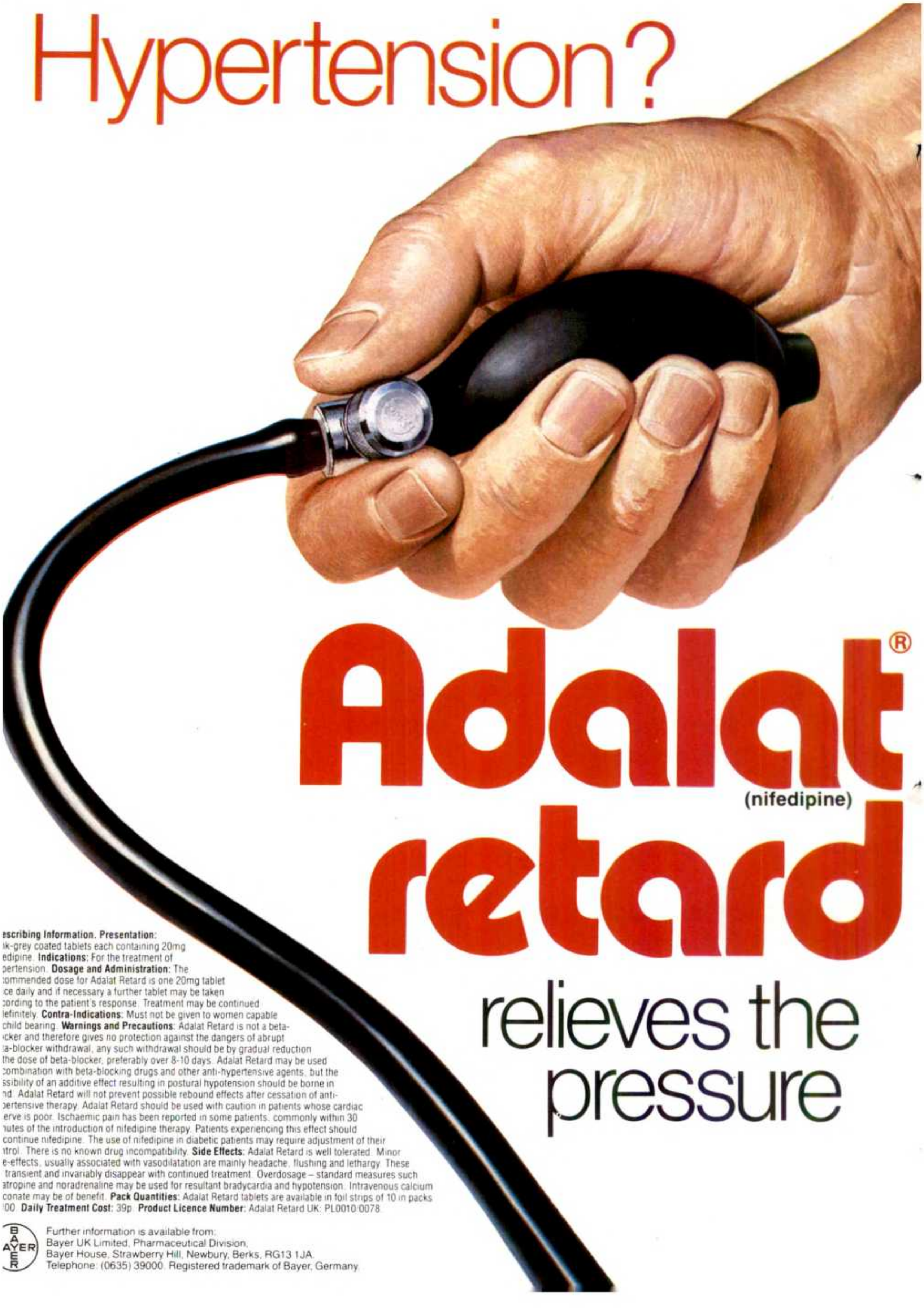

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edipine. **Indications:** For the treatment of
pertension. **Dosage and Administration:** The
commended dose for Adalat Retard is one 20mg tablet
ce daily and if necessary a further tablet may be taken
cording to the patient's response. Treatment may be continued
lefinitely. **Contra-Indications:** Must not be given to women capable
child bearing. **Warnings and Precautions:** Adalat Retard is not a beta-
cker and therefore gives no protection against the dangers of abrupt
a-blocker withdrawal, any such withdrawal should be by gradual reduction
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pertensive therapy. Adalat Retard should be used with caution in patients whose cardiac
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Br Heart J 1985; 53: 585–6

Editorial

Chronic Mobitz type I second degree atrioventricular block
Has its importance been underestimated?

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Second degree heart block traditionally is separated into subtypes considered to be clinically, pathologically, anatomically, prognostically, and therapeutically distinct.[1–8]

Mobitz type II block has been associated with an adverse prognosis through its progression to complete heart block with unstable and slow ventricular escape pacemakers. Pathological studies have indicated that the block is most usually in the His-fascicular system.

Mobitz type I block (Wenckebach block) has been regarded as much more benign. In young subjects, particularly those who are well trained, it can occur through excess vagal tone.[9] In more elderly patients, disease of the atrioventricular node has been held responsible for the arrhythmia. In the event of complete atrioventricular block escape pacemakers are expected to be stable and to operate at a reasonable rate.

Shaw *et al* present data in the current issue of the journal (p 587) which challenge some of these long held concepts. In their figures, derived from up to 14 years of follow up in a selected but geographically contained population, three and five year survival rates in unpaced patients were similarly poor regardless of the type of second degree atrioventricular block. Based on this evidence, electrocardiographic features can no longer be used to separate high and low risk patients with second degree atrioventricular block. Their review of the prognostic data for type I block highlights the paucity of evidence on which current clinical practice is based and the ease with which authoritative opinion may be established.[10]

The findings of Shaw *et al* have important therapeutic implications. In their observational study, permanent pacemaking was neither randomly nor systematically applied except as treatment for patients with major cardiac symptoms, particularly disturbances of consciousness. The significant prognostic advantage observed in paced patients leads the authors to conclude that patients with chronic type I second degree atrioventricular block "should be considered for pacemaker implantation on similar criteria to those adopted for higher degrees of block." Their observations of the results of this intervention refute a differential therapeutic approach to these subtypes of second degree atrioventricular block.

The authors, mindful of their observed 42% five year survival for unpaced patients with type I atrioventricular block, suggest that "in the absence of special circumstances" patients with this arrhythmia should be treated with pacemakers. The "special circumstances" are not specified, but the implication is that the policy for pacemaker implantation should be more liberal. We must, however, be cautious before adopting radical changes in clinical management. In the study as reported, the decision that a patient be paced or be left unpaced emerged as the most relevant prognostic factor, and the near normal life expectancy for paced patients emphasises the propriety of pacing for this group selected largely on the basis of symptoms. The study does not explore the question of whether or not the unpaced patients would have derived similar benefits from pacing. Although the results might merely support current indications for pacing in second degree atrioventricular block, the remarkably poor prognosis for unpaced patients, irrespective of the type of second degree block, forces reconsideration.

Adoption of a more aggressive pacing policy would have doubled the pacemaker insertion rate in the population reported in this study. If extrapolated to the United Kingdom, prophylactic pacing for Mobitz

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type I atrioventricular block might necessitate an extra 280 pacemaker insertions a year at a cost of £165,000. Have Shaw *et al* presented sufficiently secure evidence to support this approach? It is easy to procrastinate and to defer policy changes awaiting confirmation of controversial results. The long follow up required to assess the efficacy of intervention in this condition discourages, however, prospective investigation, and few other studies can be expected to be available within the next five or 10 years. Rather we must critically weigh this new evidence and acknowledge that Shaw *et al* present the most comprehensive information currently available for this patient population.

Scientists may await the definitive answer, but clinicians will be tempted to widen their indications for pacing in chronic second degree atrioventricular block. Fortunately, such an approach need not impede further scientific study. Implantation of a rate programmable VVI generator with a low backup pacing rate might preserve life in the event of asystole, while its activation would confirm its therapeutic value.

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Survival in second degree atrioventricular block

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SUMMARY Two hundred and 14 patients with chronic second degree heart block were seen and followed up in the Devon Heart Block and Bradycardia Survey between 1968 and 1982. The patients were divided into three groups according to the type of block. In group 1 there were 77 patients with Mobitz type I block (mean age 69 years), in group 2, 86 patients with Mobitz type II block (mean age 74 years), and in group 3, 51 with 2:1 or 3:1 block (mean age 75 years). The five year survival was similar in all groups, being 57%, 61%, and 53% in groups 1, 2, and 3 respectively. The presence or absence of bundle branch block did not appear to influence prognosis. In particular, patients in group 1 without bundle branch block did not fare any better than those in group 2 both with and without bundle branch block. One hundred and three of the patients were fitted with pacemakers, the proportion being greatest in group 2. In each group a significantly larger number of paced patients survived than unpaced. The five year survival for all the paced patients in the study was 78% compared with 41% for the unpaced. Since the paced patients were slightly younger than the unpaced two age matched groups of 74 patients each were selected from the paced and unpaced patients, but the five year survival of those paced was still significantly better.

It is concluded that in the patients in the present study chronic Mobitz type I block has a similar prognosis to that of Mobitz type II block. Unpaced patients with both types did very badly, whereas those fitted with pacemakers had a five year survival similar to that expected for the normal population. These results refute the benign reputation of chronic Mobitz type I block and imply that patients with this condition should be considered for pacemaker implantation on similar criteria to those adopted for patients with higher degrees of block.

The use of pacemakers has been a major advance in the treatment of different forms of bradycardia, and because of its dramatic effect in some groups of patients it has become the vogue. The reaction to this is the current reassessment of the place of the pacemaker in several conditions. Four years ago we produced evidence that the prognosis in chronic sinoatrial disorder (sick sinus syndrome) was not appreciably improved by pacing,[1] and recently the place of this form of treatment in high risk bundle branch block has been questioned.[2–4] Second degree Mobitz type I (atrioventricular nodal) block is widely believed to be relatively benign.[5–7] The corollary is that patients with this type of conduction disturbance do not require pacing in the absence of troublesome symptoms.[8–10] Nevertheless, the number of patients with second degree block in these studies is relatively small; furthermore, the reports come from highly specialised units, which in turn implies considerable case selection. Reappraisal of the natural history and indications for a pacemaker in partial heart block would now seem appropriate.

We report a 14 year prospective study to compare the outlook of patients with second degree Mobitz type I (atrioventricular nodal) block with that of those with Mobitz type II (distal) block, both with and without pacemakers. Recently, it has been suggested that 2:1 and 3:1 atrioventricular block may be a distinct form of second degree block.[5] Patients whose electrocardiograms consistently showed this pattern have been treated as a separate group.

Patients and methods

ELECTROCARDIOGRAPHIC DIAGNOSIS

Patients with second degree block were sought from

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Table 1 *Basic data on entry. Figures are numbers of patients unless stated otherwise*

	Patient groups			*All patients*
	1	*2*	*3*	
No in group	77	86	51	214
Mean age (yr)	69	74	75	72
Median age (yr)	72	74	77	74
Age range (yr)	25–96	44–92	31–97	25–97
Right bundle branch block	14	17	12	43
Left bundle branch block	13	19	6	38
Stokes-Adams attacks	25	40	19	84
Dizziness (short of loss of consciousness)	10	11	10	31
Chest pain on effort	18	17	9	44
"Cardiac" breathlessness	19	20	16	55
No major symptoms	35	30	16	81
Cardiac failure	4	6	6	16
Myocardial infarction	12	8	11	31
Sinus node disease	5	2	0	7
Congenital heart disease	2	2	0	4
Rheumatic fever	9	7	5	21
Diabetes	5	2	3	10
Cerebrovascular accident	9	6	5	20
Rheumatoid arthritis	10	9	5	24

the Devon Heart Block and Bradycardia Survey during the period 1968–82. This recruits by direct approach to the general practitioners in the area, from the open electrocardiographic service of the Exeter district, and from referrals to the cardiac department in Exeter by physicians of the Torbay, North Devon, and Exeter districts.[11 12] Patients with second or third degree block or unexplained bradycardia (ventricular rate below 56 beats/min) are admitted to the survey. Instances of transient block persisting for less than 28 days after acute myocardial infarction or carditis and drug induced block—in patients taking digitalis, block not persisting for more than 17 digitalis free days—are excluded.

Two hundred and fourteen of the patients seen in the survey were found to have second degree atrioventricular block on the standard 12 lead electrocardiogram, and these form the basis of the present study. Patients were divided into three groups according to the first electrocardiogram showing second degree block. Those with Mobitz type I or Mobitz type II block[13] formed groups 1 and 2 respectively. If the initial electrocardiogram showed 2:1 or 3:1 atrioventricular block but subsequent traces showed features of Mobitz type I or Mobitz type II the patient was allocated to the appropriate group. In some patients 2:1 or 3:1 block remained "fixed" and these formed group 3.

CLINICAL DETAILS

Table 1 shows the composition of the three groups. The mean and median age were lowest in group 1, although the differences from the other groups were not significant. There was a general preponderance of males, the sex ratio being 1·3 : 1 (males to females). Group 3 was unusual in having a gross reversal of the sex ratio of 0·65 : 1, the difference being significant at the 1% level. The figures for symptoms in Table 1 refer to those recorded by us on entry to the study. The complaint of breathlessness was considered to be cardiac in origin if the patient was receiving a daily dose of ≥40 mg frusemide or ≥1 mg bumetanide.

Table 2 *Numbers of patients showing a change in conduction during the survey*

Group	*BBB*		*Mobitz type I*		*Mobitz type II*		*Fixed 2:1 or 3:1 block*		*Third degree block*	
	On entry	*Later*	*On entry*	*Later*	*On entry*	*Later*	*On entry*	*Later*	*On entry*	*Later*
					Group 1					
No BBB	47		45	2	0	3	2	1	0	18
BBB	27	3	30	0	0	1	0	0	0	12
					Group 2					
No BBB	41		0	1	38	3	3	2	0	17
BBB	36	9	0	0	40	5	5	1	0	15
					Group 3					
No BBB	28		0	0	0	0	28	0	0	14
BBB	18	5	0	0	0	0	23	0	0	7

BBB, bundle branch block.

Symptomatic patients usually had more than one complaint, but 81 had no major cardiac symptoms on entry.

The reason for the patients' initial attendance to their doctor was not included in the data recorded when the survey started in 1968 and was added to the questionnaire subsequently. In the 131 patients seen during this latter period dizziness or some other disturbance of consciousness was the principal complaint in 54 patients (16 in group 1, 21 in group 2, and 17 in group 3) and coincidental non-cardiac illness was the next most common form of presentation in 29 patients (11 in group 1, 14 in group 2, and four in group 3). Other reasons for the patients seeking medical advice were breathlessness in 23, chest pain in six, routine medical examination in six, palpitation in three, and the reason for consultation could not be ascertained in 10.

SURVIVAL ANALYSIS

Survival was calculated from the date of the first observation of second degree block to the date of the last follow up examination or death, and the date of pacemaker insertion, if any, was noted. In the case of paced patients two sets of figures were derived, one dating survival from entry to the study and the other from the time of implantation.[1] In the absence of complications patients were reviewed annually with a questionnaire, physical examination, and an electrocardiogram. Every effort was made to follow patients leaving the district, but one of them, having been seen regularly for four years, was lost. Survival was analysed by the life table method.[14] Survival curves were compared year by year over a five year period using the Lee-Desu statistic,[15 16] and mortality figures for a normal population of the same age and sex distribution were calculated from the Registrar General Decennial Supplement.[17]

Results

CHANGES IN CONDUCTION

Few patients (five) changed from Mobitz type I to Mobitz type II, or vice versa, during the study and only 14 patients in groups 1 and 2 had episodes of 2:1 or 3:1 block (Table 2). Improvement in conduction to first degree block or normal conduction occurred in 35 cases. In 83 patients there was transient or persistent deterioration to third degree block. Bundle branch block was present in 98 patients, usually on entry, but in 17 it developed during the study.

Twenty patients developed Stokes-Adams attacks after entry to the study (seven each in groups 1 and 2 and six in group 3), and other major cardiac symptoms occurred in a further six patients. One hundred and three patients were fitted with pacemakers, the numbers in the groups being 33, 49, and 21 in groups 1, 2, and 3 respectively. Most patients were paced to prevent disturbance of consciousness, and this or another major cardiac symptom was present in 29, 41, and 18 of the paced patients in groups 1, 2, and 3 respectively. Three patients were paced to allow them to drive a car and 12 because of minor symptoms.

SURVIVAL DATA

The overall survival of patients in all groups was essentially similar (Table 3; Figure and Table 4), the median being 69 months. Paced patients fared considerably better than those unpaced in all groups. In group 1 the percentage survival at five years was 78 for paced subjects (dating survival from entry to the study) compared with 42 for unpaced subjects ($p<0{\cdot}01$), in group 2 the figures were 73 and 48 respectively ($p<0{\cdot}015$), and in group 3 they were 86 and 31 respectively ($p<0{\cdot}001$). Table 3 also compares the survival of paced and unpaced patients pooling the data from groups 1, 2, and 3. The paced patients had a very much better outlook, but the two sets were not identical in respect of age since more of the younger patients were paced than the older patients (mean age difference 5 years). To reduce the age imbalance the paced and unpaced groups were both stratified by age, and randomised deletions were made so as to equalise the numbers of paced and unpaced patients within each age band. This process produced paced and unpaced subsets, each having 74 members. Age matching improved the five year survival of the unpaced patients from 41% to 49%. Nevertheless,

Table 3 *Percentage survival in the three groups for paced and unpaced patients. Values are mean (SEM)*

Group	*Survival at three years*				*Survival at five years*				*Signifiance (p)*	
	All patients	*Unpaced*	*Paced**	*Paced†*	*All patients*	*Unpaced*	*Paced**	*Paced†*	*Paced* vs unpaced*	*Paced† vs unpaced*
1	63·6 (5·8)	50·6 (7·9)	83·0 (6·9)	82·7 (7·1)	56·5 (6·2)	41·9 (8·0)	78·4 (7·9)	78·1 (8·0)	<0·01	<0·013
2	69·7 (5·5)	59·5 (8·7)	77·8 (6·6)	74·3 (7·1)	61·4 (6·2)	47·6 (9·3)	73·3 (7·6)	74·3 (7·1)	<0·015	<0·05
3	65·1 (7·3)	45·7 (9·9)	94·2 (5·7)	92·8 (8·2)	52·6 (8·2)	30·5 (9·8)	85·6 (9·7)	87·5 (13·7)	<0·001	<0·002
Pooled data	66·3 (3·5)	48·8 (5·1)	82·8 (4·1)	79·8 (4·4)	57·5 (3·9)	41·0 (5·2)	77·5 (4·8)	74·0 (5·2)	<0·0001	<0·0001

*Survival calculated from the date of entry into the study.
†Survival calculated from the date paced.

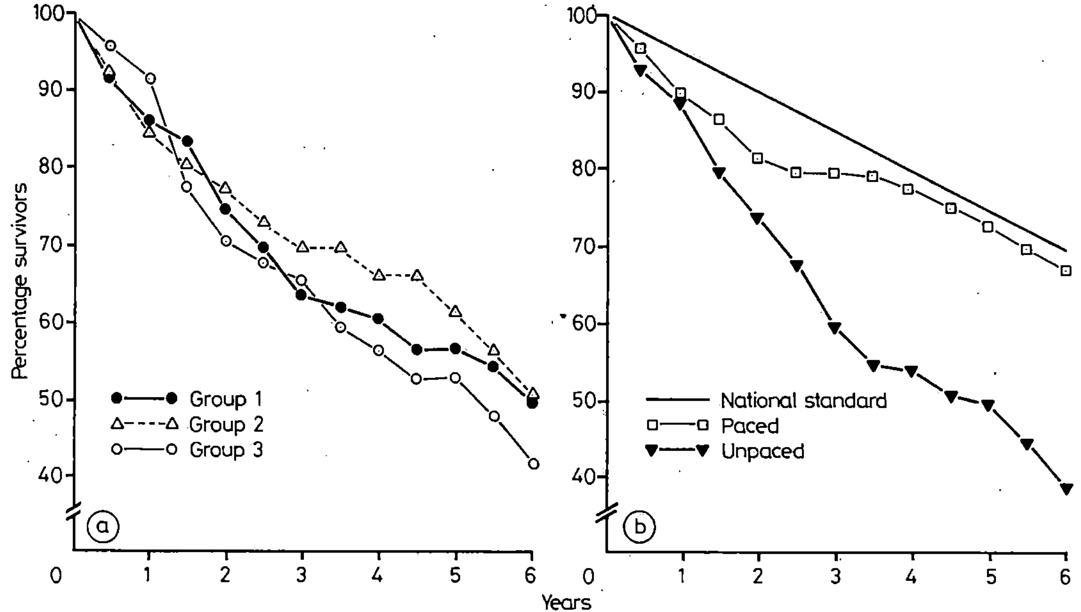

Figure *(a) Overall survival of patients in the three different groups in relation to time in years since admission to the study. The curves are taken to six years to show that there are no sudden changes in the trends after the initial five years. (b) Survival of paced patients compared with that of unpaced patients. In both cases the time in years was estimated from the date of entry to the study. An additional line is plotted which represents the expected survival for the general population (National Standard) of similar age and sex.*

they remained significantly worse off ($p<0·015$) than the paced patients, in whom the five year survivals were 72% when dated from admission to the study and 67% when dated from the time of pacemaker implantation. The Figure shows the survival data in the age matched paced and unpaced patients. A further curve is shown which represents the expected survival of a group of normal subjects of similar age and sex (National Standard) to the patients in this study. This line closely approximates that for the paced patients.

Table 4 *Percentage survival data for the three groups of patients illustrated in Fig. 1. The effective sample sizes are given in brackets at annual intervals*

Time intervals (mnth)	*Group 1*	*Group 2*	*Group 3*	*Pooled data*
0	100·0 (77)	100·0 (86)	100·0 (51)	100·0 (214)
3	93·2	93·8	100·0	95·0
6	91·8	92·5	95·6	93·0
9	90·4	87·2	91·1	89·3
12	86·2 (64)	84·5 (66)	91·1 (41)	86·7 (171)
15	83·3	83·2	82·0	83·0
18	83·3	80·4	77·3	80·8
21	78·9	78·9	70·2	76·9
24	74·4 (53)	77·5 (55)	70·2 (29)	74·6 (137)
27	72·9	77·5	70·2	74·1
30	69·9	73·0	67·7	70·6
33	65·2	71·4	67·7	68·2
36	63·6 (42)	69·7 (44)	65·1 (26)	66·3 (112)
39	62·0	69·7	65·1	65·7
42	62·0	69·7	59·2	64·3
45	60·3	67·9	56·1	62·3
48	60·3 (35)	66·0 (36)	56·1 (18)	61·5 (89)
51	56·5	66·0	52·6	59·3
54	56·5	66·0	52·6	59·3
57	56·5	63·8	52·6	58·4
60	56·5 (27)	61·4 (28)	52·6 (13)	57·5 (68)
63	56·5	56·3	52·6	55·6
66	54·2	56·3	47·8	53·7
69	49·6	50·5	47·8	49·6
72	49·6 (21)	50·5 (16)	42·8 (10)	48·6 (47)

Degree of block—Patients showing a change in degree of block, either towards improved conduction or to complete block, did not fare worse than those whose degree of block remained stable. Bundle branch block was not associated with any major difference in survival. The survival of all patients with and without bundle branch block was 62% and 70% at three years and 58% and 56% at five years. There were no important differences between patients with and without bundle branch block in the three groups. In particular, the three and five year survivals of the 47 patients in group 1 without bundle branch block (72% and 60% respectively) were similar to those of the patients in group 2 (70% and 61% respectively).

Risk factors—The potential risk factors of myocardial infarction and cardiac failure were not associated with significant differences in survival, but the numbers of patients with these conditions were small. In the non-paced patients there was a significant difference in survival ($p<0{\cdot}01$) between those with Stokes-Adams attacks and those without, being 31% and 65% at three years and 25% and 51% at five years. The majority of patients with attacks were, however, paced, whereas those without were usually not paced, so that the overall effect of Stokes-Adams attacks on prognosis was reduced (the three and five year survival of those with attacks being 59% and 53% and those without being 73% and 62% respectively). There was no significant difference between the survival of patients with and without major cardiac symptoms, being 65% and 68% at three years and 58% and 56% at five years, but again there was a difference in the proportion of paced patients.

Pacing—Patients without major cardiac symptoms had a poor prognosis when left unpaced, with an overall three and five year survival of 59% and 45% respectively. There were some variations in the chances of survival in the three groups, but in all of them patients without major symptoms fared badly if they were not paced. In groups 1 and 2 the five year survivals were 48% and 49% respectively, and the mean ages of the unpaced patients without major symptoms were similar to that of the parent groups, being 67 and 75 years respectively. Unpaced patients without major symptoms in group 3 were rather older than the mean age for the group as a whole, the mean age being 80 years, and there was insufficient data to calculate survival at five years but the three year survival was only 29%.

Discussion

In 1968 Langendorf and Pick made a plea for the clinical distinction between type I and type II atrioventricular block on the routine electrocardiogram.[18] They considered this to be of particular value in the immediate postmyocardial infarction period, because they found that the prognosis of type I was much better than that of type II. With the introduction of the technique of His bundle electrocardiography several workers pointed out the potential fallibility in the use of the surface electrocardiogram to locate the site of block.[19-21] Nevertheless, classification on the basis of the surface electrocardiogram still appears to be generally acceptable. Goldreyer comments, "fortunately His bundle electrocardiography has shown that the location of the block is generally apparent from the electrocardiogram . . . . .",[22] and in 1979 Zipes wrote, "although the classification is descriptive, clinically separating second degree AV block into type I and type II serves a useful function and in most instances the differentiation can be made easily and reliably from the surface ECG."[6]

The similarity in outlook between patients with Mobitz type I and Mobitz type II second degree atrioventricular block in our study is at variance with current opinion.[10] Even patients with Mobitz type I block without bundle branch block, who previously were considered to have an optimum prognosis,[6] had a five year survival that was no better than that of patients with Mobitz type II block. Contrary to views expressed in published reports,[23] Stokes-Adams attacks were common in patients with Mobitz type I block in this series. Before discarding these results as a statistical quirk, we propose to review the evidence on which the present consensus is based.

In their report the American College of Cardiology and Heart Association Task Force on assessment of cardiovascular procedures concluded that Mobitz type I second degree atrioventricular block, when due to nodal delay, was relatively benign[24] and refer to three authoritative studies.[5 7 8] Donoso *et al* reviewed 11 patients with second degree block discovered in 100 consecutive cases of Stokes-Adams syndrome.[5] There were three patients with Mobitz type II block, one of whom died a year after initial assessment and another required a pacemaker. The other eight cases were of "more advanced atrioventricular block," varying between 3:1 and 5:1. Two of these patients died in hospital, and three more died in the next 12 months. They do not describe any patients with Mobitz type I block. Dhingra *et al* reported 15 patients with second degree atrioventricular block and bundle branch block, four of whom had Mobitz type I block.[8] They concluded that the clinical course in most of such patients would be "malignant," with most needing pacemakers whether the block was proximal or distal to the His bundle, and three of their patients with Mobitz type I block required pacemaker therapy. Strasberg *et al* reported 56 patients with chronic second degree atrioventricular block, fol-

Table 5 *Second degree atrioventricular block recorded by ambulatory electrocardiographic monitoring in studies of normal subjects*

Author	*Subjects*		*Mobitz type I*	*Mobitz type II*
	No	*Age (yr)*		
Scott *et al*[31]	131	10–13 (range)	14	0
Viitasalo *et al*[32]	35	23·0 (5·8) (mean (SD))	2	0
Brodsky *et al*[33]	50	23–27 (range)	3	0
Sobotka *et al*[34]	50	22–28 (range)	2	0
Clarke *et al*[35]	86	16–65 (range)	2*	1*
Clee *et al*[36]	50	Over 50	1	1
Camm *et al*[37]	98	Over 75	0	0

*One subject common to both.

lowed up for periods of between 157 and 2280 days.[7] They differentiated between those with and those without associated organic heart disease and found the latter to have a relatively benign cause. Nevertheless, this was a small group of only 19 patients, of whom seven were trained athletes and 12 were under 35 years old. Even in this rather unusual group six had had one or more syncopal attack, two were fitted with pacemakers during the study, and two died "non suddenly." Most of their patients (37) had organic heart disease, 16 of whom died during the study (10 were paced and five of these died during follow up). The reports sited above show the potentially dangerous nature of Mobitz type II second degree block, but the evidence that chronic Mobitz type I block is relatively harmless is far from definite.

Recent studies imply that the pathological distinction between Mobitz type I and Mobitz type II block if often blurred. Certainly, anatomical lesions in the conducting system show poor correlation with the electrocardiogram,[25, 26] and this is not always greatly improved when the His bundle electrocardiogram is used to locate the block.[27] Ohkawa *et al* reviewed the histology of the conducting system in five patients with narrow QRS complexes and block proximal to the His bundle deflection (AH block) and four patients with wide QRS complexes and block distal to the His bundle deflection (HV block).[28] In the former, the main pathological change was found in the branching portion of the bundle in three of the five patients. The authors conclude that AH block resulted not only from lesions in the upper part of the His bundle but also from lesions in the branching portion.

Surveys of normal subjects, using standard electrocardiography, indicate that second degree atrioventricular block is very rare,[29, 30] but Mobitz type I block has been recorded on ambulant electrocardiograms in some normal people. The conduction disturbance is transitory, usually occurring at night, and is principally seen in young subjects (Table 5). This phenomenon, commonly ascribed to excessive vagal tone, is unlikely to be confused with the persistent second degree block occurring in the elderly patients of the present study, although, possibly, it may have played a part in some of the young athletes studied by Strasberg *et al*.[7] The current study specifically excluded instances of transient Mobitz type I block, resulting either from digitalis toxicity or acute myocardial infarction, which may have a better prognosis than that of chronic idiopathic atrioventricular block. The natural history of chronic heart block is multifactorial,[38] and it is possible that a subset of patients with the features of Mobitz type I second degree block on the standard electrocardiogram have a good prognosis. No such group could, however, be identified in the present study, and analysis of the potential risk factors did not indicate any method of detecting low risk subjects.

Patients in group 3 with fixed 2:1 and 3:1 atrioventricular block fared similarly to those in the other groups. The site of block in this group has traditionally been considered to be in the bundle branches,[39] a view supported recently by His bundle electrocardiograms.[8] The one major difference between group 3 and the rest was the considerable predominance of women in group 3. Men exceed women in most published studies of heart block, but Kulbertus *et al* found women to predominate in one subgroup of interventricular block.[40]

We conclude that a review of three key references does not present convincing evidence of a good risk group of patients with Mobitz type I second degree block. The main objectives for pacemaker therapy, in heart block, are to improve the chances of survival and prevent troublesome symptoms, in particular Stokes-Adams attacks. In all three groups in the present study, paced patients lived longer than unpaced, the difference being significant both in Mobitz type I and Mobitz type II block. Even patients without major symptoms fared badly if left unpaced. Inevitably, since this was not a randomised controlled trial of pacing, the paced and unpaced patients were not comparable in all respects. Nevertheless, no major risk factor appeared to predominate in the unpaced patients at the expense of the paced. Stokes-Adams attacks occurred in almost half of the patients in each of the three groups studied. Current advice is that, in the absence of special circumstances, patients with chronic Mobitz type II second degree block should be treated with pacemakers. This study implies that a similar approach should be adopted in cases of chronic Mobitz type I second degree block.

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Persistent atrial standstill in familial Ebstein's anomaly

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SUMMARY Persistent atrial standstill occurred in a father and his youngest son with familial Ebstein's anomaly. In both cases routine electrocardiograms showed no atrial electrical activity and cross sectional echocardiograms showed inferior displacement of the septal tricuspid leaflet and tethering of the tricuspid leaflets to the right ventricle. The father had a cerebral embolism and died of a myocardial infarction. Necropsy showed attachment of the septal tricuspid leaflet below the membranous septum. On serial histological examination fibrofatty infiltration of the right atrial wall, the atrioventricular node, and the inferior part of the His bundle up to the bifurcation was present. The son had haemodynamic and electrophysiological findings consistent with mild Ebstein's anomaly and persistent atrial standstill, for which permanent cardiac pacing was necessary.

The persistent atrial standstill with slow escape rhythm was most probably a consequence of the abnormalities in both the atrial wall and the His bundle which, together with the abnormal attachment of the tricuspid valve, may be features of the same congenital cardiac anomaly.

Ebstein's anomaly is an uncommon congenital heart disorder[1] predisposing to right bundle branch block, pre-excitation,[2] and an increased risk of sudden cardiac death.[3 4] Atrial fibrillation occurs in one third of patients with Ebstein's anomaly[3] but to our knowledge atrial standstill has never been reported in this condition. A familial occurrence has been reported independently for atrial standstill[5–7] and for Ebstein's anomaly.[8–10]

We report the rare association of familial Ebstein's anomaly and persistent atrial standstill in a father and son.

Patients and methods

CASE 1

A 31 year old man presented in 1956 with transient aphasia and right hemiparesis. Two other episodes of aphasia occurred during the following years, and he was referred to a physician in 1964 because of a return of the right hemiparesis and aphasia, which were slow to improve.

Physical examination showed a regular pulse of 48 beats/min, normal heart sounds, and a slight right facial paresis. The electrocardiogram showed junctional regular rhythm with left QRS axis deviation and absent initial septal forces. No P waves were visible (Fig. 1). An intra-atrial electrogram detected no atrial electrical activity. The escape rhythm was atrioventricular junctional at a regular rate of 50 beats/min.

Right heart catheterisation showed no "a" waves in the right atrial pressure tracings. No atrial wall movement was observed at fluoroscopy. No angiogram was performed.

The patient was discharged taking oral anticoagulants. Simultaneous M mode echocardiograms of the tricuspid and mitral valves were recorded from the parasternal transducer position, and tricuspid valve closure followed mitral valve closure with an interval of 50 ms. There was no A wave on the mitral and tricuspid valve echocardiograms. A cross sectional echocardiogram in the apical and subcostal four chamber views showed an abnormally low septal insertion of the septal tricuspid leaflet, enlargement of the right atrium, increased redundance of the tricuspid subvalvar apparatus, and tethering of the leaflets. In July 1981 he had an anteroseptal myocardial infarction and died as a result of cardiogenic shock. At necropsy no thrombus was found in the coronary arteries. A large infarct of the septal and anterior wall

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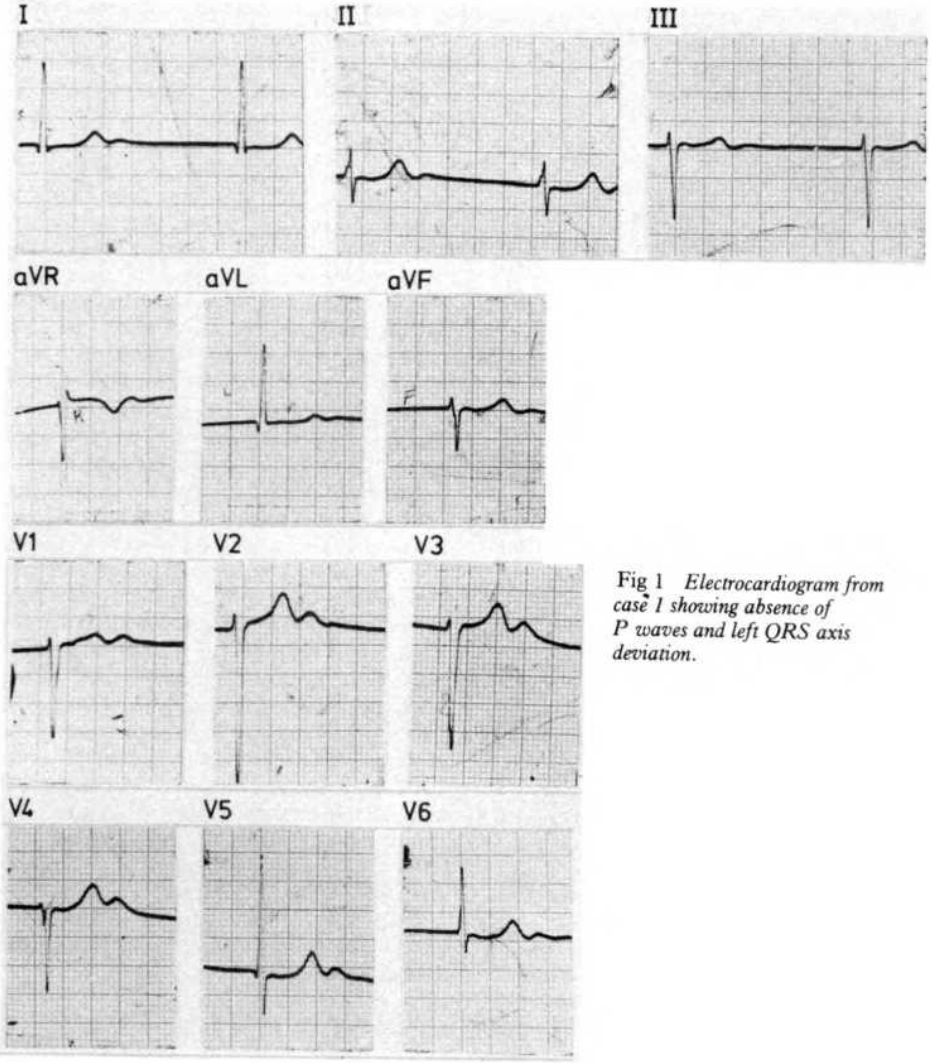

Fig 1 *Electrocardiogram from case 1 showing absence of P waves and left QRS axis deviation.*

was present with a septal rupture of 3 cm in diameter obstructed by a thrombus extending into the right ventricle. The septal leaflet of the tricuspid valve was attached to the ventricle 1 cm below the membranous septum (Fig.2).

Histological examination of the heart was performed. The sinoatrial and atrioventricular nodes and their approaches, the atrioventricular bundle, and bundle branches were serially sectioned perpendicular to the long axis of the sinoatrial node and of the His bundle. Every tenth section was retained. Alternate sections were stained with haematoxylin and eosin and the Azan-Heidenhain (variation of Masson-Trichrome) stain.[11] There were 350 sections in the sinus node and 1500 sections in the atrioventricular bundle region. Microscopical examination showed a fresh infarct and diffuse fibrotic scars in both ventricles. The right atrial wall was almost completely replaced by fibrofatty infiltration, and there was no distinct sinus node structure. Fibrofatty infiltration was seen in the approaches of the atrioventricular node. The compact atrioventricular node, with disorganised cells, was located to the right of the central fibrous body. The atrioventricular bundle was at the ventricular level, on the right, above the tricuspid connection.

Slightly fatty fibrosis was found on the inferior part of the His bundle. This fatty fibrosis was increasingly

Fig 2 *Case 1: histological section of the atrioventricular junction at the level of bifurcation. The His bundle is at the upper right of the muscular septum. The tricuspid valve is attached 1 cm below the membranous septum. (Haematoxylin and eosin × 7, original magnification.)*

evident and became subtotal at the end of the bifurcation. The left main bundle was intact, but an interruptive fibrosis was seen in its anterior and septal ramifications. The right bundle was intact.

CASE 2

The youngest son of the patient in case 1 was born in 1952. Although asymptomatic, he was referred to a physician because of a cardiac murmur. A splitting of the two heart sounds, a third heart sound, a soft systolic ejection murmur, and a mild diastolic murmur at the left sternal border were heard. The electrocardiogram showed sinus rhythm with supraventricular extrasystoles, first degree atrioventricular block (PR interval 0·35 s), and incomplete right bundle branch block.

At cardiac catheterisation, normal pressures in the heart chambers and a moderate left to right shunt of 1·65:1 at atrial level were found. Withdrawal of a pacing electrode from the right ventricle to the right atrium showed an electrical pressure pattern consistent with Ebstein's anomaly.[12]

Left atrial angiography detected a secundum atrial septal defect. The right ventricular angiogram showed a displaced tricuspid valve, demarcating an atrialised and a functional right ventricle. There was moderate tricuspid regurgitation (grade II). In 1978, the patient became dyspnoeic on exertion and in 1980 was referred for further evaluation.

Physical examination showed no cyanosis. His blood pressure was 120/80 mm Hg and his pulse regular at 44 beats/min. Heart sounds were unchanged. The electrocardiogram showed the absence of P waves, and regular ventricular complexes occurred at a rate of 40 beats/min with a complete right bundle branch block pattern. Continuous electrocardiographic monitoring showed heart rates ranging from 22 to 120 beats/min without P waves and an episode of ventricular tachycardia. An electrophysiological study showed a complete absence of atrial activity (Fig. 3). Right atrial pacing with stimuli of up to 15 mA and pulse width up to 2 ms did not result in atrial capture. Lack of atrial activity and atrial inexcitability indicated atrial standstill.[13] A permanent pacemaker was inserted leading to the disappearance of symptoms.

M mode echocardiography showed a delay in closure of the tricuspid valve of 70 ms compared with mitral valve closure. Cross sectional echocardiography showed inferior displacement of 14 mm of the septal tricuspid leaflet in the apical four chamber view. The tricuspid valve was slightly thickened, and the anterior and septal leaflets were tethered to the right ventricle.

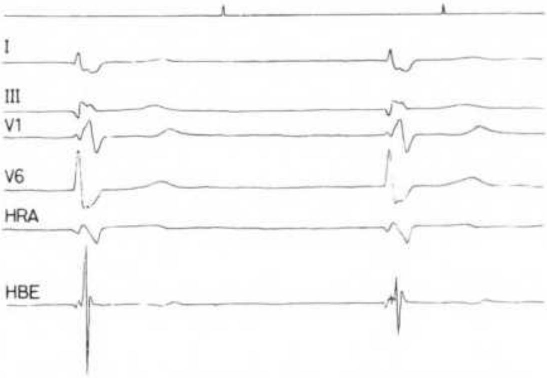

Fig 3 *Simultaneous electrocardiogram, high right atrium (HRA) electrogram, and His bundle electrogram (HBE) showing the complete absence of atrial activity.*

Discussion

Atrial standstill is characterised by the absence of P waves on the standard and endocavitary electrocardiograms, a slow, regular, supraventricular escape rhythm, a lack of atrial excitability, and an absence of atrial contraction and atrial pressure changes.[14] Atrial standstill may be transient or persistent. Persistent atrial standstill is a rare condition. A review of published reports identified 23, of which 15 were isolated cases. A familial occurrence has been reported in a small mountain community in which marriages between siblings had often taken place over several generations.[7] To our knowledge, this is the first case reported in association with Ebstein's anomaly.

The proposed mechanisms for atrial standstill include atrial degenerative disease[15] or combined atrial and bundle branch disease,[13] such as in our case. In this respect the haemodynamic stress induced by the tricuspid anomaly, such as in rheumatic tricuspid disease, may have produced the abnormalities seen in both the atrial wall and the His bundle. The associated atrioventricular bundle abnormalities contributed to the slow escape rhythm.

Familial Ebstein's disease is rare,[8-10] and the anomaly is best considered as a failure of delamination of the septal leaflet. It is therefore not surprising for the atrioventricular bundle to be located above the valve attachment, as in our case.

It cannot be excluded that some of the 40 patients with persistent atrial standstill previously reported could have had a mild form of Ebstein's anomaly. In fact, because of the absence of electrical atrial activity, intracavitary electrocardiographic and pressure relations are difficult to interpret. A right ventriculogram was rarely performed in the reported cases. Cross sectional echocardiography was not performed in the recent reports. This technique seems, however, to be the most useful in diagnosing the milder forms of Ebstein's anomaly.[16 17] We suggest that patients with persistent atrial standstill should be examined by cross sectional echocardiography in the four chamber view to detect dysplasia of one or two atrioventricular valves.[18]

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Increased diastolic blood pressure response to exercise testing when coronary artery disease is suspected

An indication of severity

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SUMMARY One hundred and two consecutive patients with a history of chest pain or recent previous myocardial infarction underwent maximal treadmill stress testing and coronary angiography. The diastolic blood pressure response to exercise was evaluated independently of ST segment change and systolic blood pressure. In the presence of a normal systolic blood pressure response an increase in diastolic blood pressure of 15 mm Hg on at least two determinations during the same stage of exercise was considered abnormal. In 99 patients an accurate diastolic reading was possible. Of these, 61 had a normal diastolic blood pressure response; in 25 of these the ST segment was ischaemic and seven had three vessel coronary artery disease. Thirty eight patients had an abnormal diastolic blood pressure response and 27 of these had an ischaemic ST response. Of the 11 with a negative ST response for ischaemia one had left main stem disease, seven three vessel disease, and three two vessel disease. Patients with an abnormal diastolic response had greater ST depression with more angina at a reduced workload than those with a normal diastolic response.

In patients with chest pain an abnormal increase in diastolic blood pressure on exercise reflects severe coronary artery disease. Although no false positives occurred in this study there was an appreciable number of false negatives (sensitivity 46%) in both patients with chest pain and those with infarction. An abnormal diastolic response therefore represents a useful additional diagnostic indicator of coronary artery disease when the ST segment response is normal or borderline. When the diastolic pressure becomes increased with or without ST changes the likelihood of severe coronary artery disease is increased.

Normally during exercise the diastolic blood pressure decreases owing to a fall in the systemic vascular resistance secondary to peripheral vasodilatation.[1] Previous studies have shown that the response of the systolic blood pressure to exercise testing has its own useful diagnostic implications. There is normally a graded rise during maximal exercise treadmill testing, whereas a failure to rise or a fall during exercise suggests significant left ventricular ischaemia.[2–5] At present, ST segment abnormalities, the systolic blood pressure response, and angina are accepted variables for assessing the results of exercise testing. Nevertheless, there remain some borderline cases in which interpretation is difficult and an indication of the severity of underlying disease uncertain.

In looking for other diagnostic variables we hypothesised that a severely ischaemic left ventricle might on exercise suffer a sufficient fall in cardiac output that a reflex increase in peripheral resistance would increase the diastolic blood pressure. We were supported in the hypothesis by the animal work of Coote and his colleagues[6] and additional experimentation in man.[7–10] We therefore evaluated the diastolic blood pressure response to exercise in 102 patients with chest pain looking at its independent diagnostic role but more importantly at its additive position with regard to the established ST and systolic blood pressure criteria. We were particularly concerned to prove or disprove its theoretical physiological reflection of significant ischaemia.

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Patients and methods

STUDY POPULATION

One hundred and two patients were studied. Twenty were undergoing routine assessment after myocardial infarction, and the remaining 82 had chest pain believed to be of cardiac origin. All were studied by maximal treadmill stress testing using 12 lead electrocardiography, and coronary angiography. Table 1 shows the patients' characteristics and clinical data. Only patients with a normal resting blood pressure were included. No patient received cardioactive drugs for 48 hours before the tests, and none was taking digoxin.

EXERCISE TESTING

Control electrocardiograms and blood pressure measurements were obtained with the patient standing. Twelve lead treadmill stress testing was performed, adopting the Bruce protocol.[11] Electrocardiograms were obtained at one and three minutes of each stage of the protocol, at peak exercise, and 1, 2, 3, and 5 minutes into the recovery period. The recordings were made with a fully automated programmable three channel electrocardiograph (Marquette Instrument Co, Model 1800 Treadmill EC MAC 1) complying with American Heart Association standards. The ST response was considered abnormal if ≥1 mm of downsloping ST depression persisted for five consecutive complexes 0·08 s beyond the R wave. Blood pressure was recorded by a standard sphygomomanometer cuff technique before, during, and after exercise. Diastolic blood pressure was measured at phase V. A normal response was defined as no change or a decrease in diastolic blood pressure associated with a rising systolic blood pressure. An abnormal response was defined as an increase of ≥15 mm Hg in diastolic blood pressure on two separate determinations during the same stage of exercise. The mean of two separate exercise determinations at peak exercise and <20 s into recovery was used to calculate the change in diastolic blood pressure from baseline. Diastolic pressure could not be accurately measured in three patients, leaving 99 patients available for further analysis.

ANGIOGRAPHY

All patients underwent cardiac catheterisation and coronary angiography within six to 10 weeks of the exercise test. A luminal narrowing of >70% in any of the three coronary vessels was considered to be significant and used as the criterion for diagnosing coronary artery disease.

STATISTICAL ANALYSIS

Clinical, exercise, and coronary angiographic data on the 99 patients are expressed as mean (SEM) or mean (SD). Differences between continuous variables were assessed by the two tail *t* test and unpaired *t* test.

Results

EXERCISE DATA

In 38 patients the diastolic blood pressure response to exercise was classified as abnormal, and in 61 the response was normal. Of those with an abnormal diastolic response, the specificity was 100% with no false positive cases of coronary artery disease. The sensitivity was 46% with a predictive value of 46%. Of those with a normal diastolic response and coronary artery disease, 24 had single vessel disease, and in 20 of these it subtended a previous myocardial infarction. With regard to disease greater than single vessel disease the sensitivity was 65% and predictive value 61%.

The ST responses judged independently gave a specificity of 65% and sensitivity of 32%. A negative exercise ST response, however, occurred in 20 of 22 patients with single vessel disease subtending a previous myocardial infarction. In this setting the ST response was accurately predicting the absence of additional disease. The degree of ST abnormality was greater in patients with an abnormal diastolic response (1·48 (1·7) *vs* 0·93 (0·16) mm, $p<0.05$) (Fig. 1). In addition, there were more patients developing angina at a reduced exercise time in the group with an abnormal diastolic response than in that with a normal response (5·3 (1·8) *vs* 7·6 (1·7) min, $p<0.001$) (Fig. 2). Eleven of the 38 patients with an abnormal diastolic response had no significant ST change on exercise. Angiography showed significant coronary artery dis-

Table 1 *Patients' characteristics and clinical data*

	Normal response (n=61)	*Abnormal response (n=38)*	*p value*
Mean (SD) age (yr)	48 (8)	51 (7)	NS
Sex (% of males)	89	87	NS
No (%) with previous myocardial infarction	35 (57%)	22 (58%)	NS
Mean (SD) resting heart rate (beats/min)	84 (3)	86 (2)	NS
Mean (SD) resting blood pressure (mm Hg)			
Systolic	126 (17)	136 (17)	NS
Diastolic	79 (8)	82 (8)	NS

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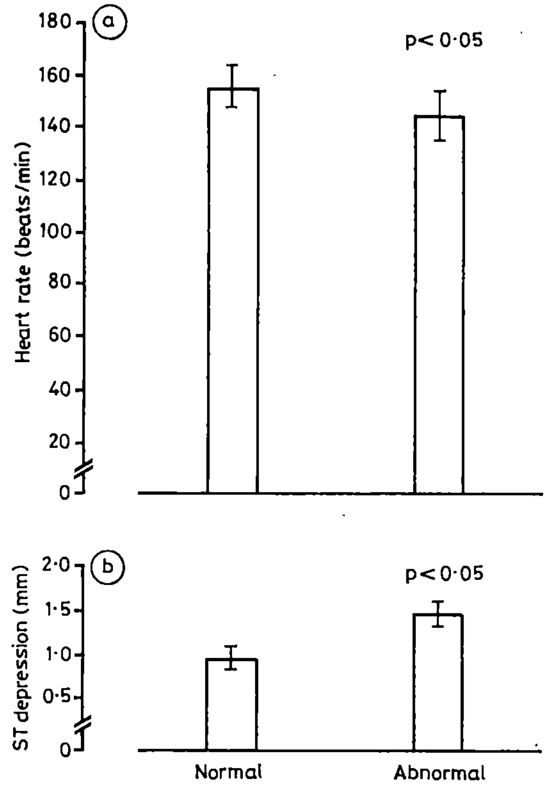

Fig. 1 *(a) Heart rate and (b) ST segment depression at peak exercise in patients with normal and abnormal diastolic blood pressure response to exercise.*

ease in all 11 patients.

The systolic blood pressure response was normal for both groups. In those with a normal diastolic response the mean systolic blood pressure rose from 126 (17) to 151 (25) mm Hg and in those with an abnormal diastolic response from 136 (17) to 163 (24) mm Hg (NS).

ANGIOGRAPHIC DATA

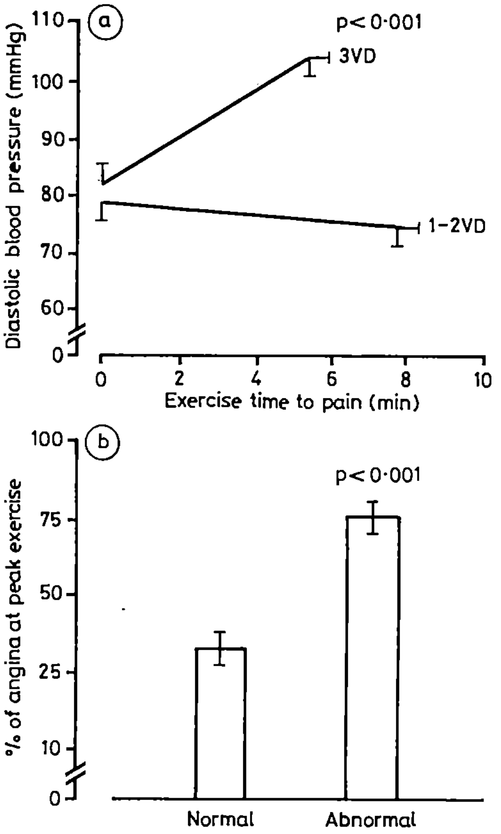

Fig. 2 *(a) Exercise time to pain and (b) percentage of angina occurring at peak exercise in patients with normal and abnormal diastolic blood pressure response to exercise. VD, vessel disease.*

At angiography, of the 61 patients who had a normal diastolic blood pressure response to exercise, 37 (61%) had one or two vessel coronary disease, seven (11%) three vessel coronary disease, and the remaining 17 (28%) non-significant coronary lesions (Table 2). In contrast, 29 (76%) of the 38 patients with an abnormal diastolic blood pressure response had three vessel or left main stem coronary disease, and only nine (24%) had two vessel coronary disease. The difference in the proportion of patients in each group with no significant coronary artery lesion and three vessel or left main stem coronary artery disease was significant ($p<0\cdot02$), and when the disease in each group was compared with the results of the diastolic pressure response the difference became highly significant ($p<0\cdot001$). Thus, those patients with an abnormal diastolic blood pressure response to exercise were more likely to have severe coronary artery disease than those with a normal response. The number of patients who had segmental contraction abnormalities on left ventriculography was similar in both groups.

Table 2 *Prevalence (%) of coronary artery disease in 38 patients with abnormal diastolic blood pressure and in 61 with normal diastolic blood pressure response to exercise*

Coronary artery disease	*Abnormal*	*Normal*
One to two vessel	24	61
Three vessel	71	11
Left main stem	5	0
Non-significant	0	28

Discussion

In the assessment of chest pain believed to be of cardiac origin the exercise electrocardiogram is of diagnostic and prognostic importance. The ST segment response alone indicates a sensitivity of between 78% and 96%, with a specificity averaging 90%.[12 13] Differences in technique and patient selection explain the variability with Fox *et al* who achieved better figures with precordial mapping.[13] Because many of our patients had single vessel disease subtending a previous infarct and no additional ischaemia our sensitivity figures including this group were poor at 32%. When allowance is made for this subgroup, however, the figure rises to a more acceptable 79%.

As this was a prospective study of consecutive exercise tests a major variability in patient selection occurred. We were principally addressing the concept of severe ischaemia so compromising left ventricular function that diastolic pressure would rise secondary to increased peripheral vasoconstriction. Our observations support this hypothesis, but by diluting our cases with the less severe we have fortunately been able to place the role of the diastolic pressure in perspective. Firstly, it is essential to define raised diastolic pressure. We selected 15 mm Hg for two reasons; firstly, we found it difficult in the clinical setting to assess accurately the diastolic pressure within 5–10 mm Hg of baseline, and, secondly, Wolthuis *et al*, studying normal adults, concluded that any rise or fall in diastolic pressure was unlikely to exceed 10 mm Hg.[1]

Previous studies make little reference to the diastolic blood pressure measurements during exercise other than to confirm the tendency to fall secondary to systemic vasodilatation.[13] Emphasis is on a fall in systolic pressure of ≥10 mm Hg[14] reflecting severe two or three vessel disease rather than single vessel disease.[15] We speculated that before this fall occurs compensatory vasoconstriction might increase the diastolic pressure so warning of imminent left ventricular compromise.

Addressing the role of the diastolic response alone in diagnosis it is clear that it is limited by the large number of false negatives. When abnormal, however, it appears to be 100% accurate in identifying underlying significant disease. It may be, of course, that it merely reflects significant left ventricular dysfunction from any cause, and we would expect an incidence of false positives for coronary artery disease but true positives for left ventricular compromise to develop with more diffuse populations studied. In patients with chest pain it is therefore primarily an index of severity reflecting significant left ventricular dysfunction secondary to ischaemia and perhaps urgency with a view to angiographic evaluation.

Combining the diastolic response with the ST response adds a valuable diagnostic variable. In those with a normal diastolic response and two or three vessel coronary artery disease the exercise ST response failed to detect one of 19 patients (Table 3). In those with an abnormal diastolic response the ST change alone failed to identify 11 of 38 (29%) patients. In all of these the diastolic response was abnormal and the severity of the problem identified. It may be argued that this ST response is poor, and we would agree. Nevertheless, the abnormal diastolic group suffered more pain at a lower workload, and it is possible that in this situation the diastolic changes preceded the ST changes because the primary reflection of ischaemia was a profound fall in cardiac output. We excluded patients with an abnormal systolic blood pressure response so that the diastolic pressure changes could be viewed independently.

In conclusion, in patients with chest pain we believe an abnormal diastolic blood pressure rise of ≥15 mm Hg is a useful and important index of underlying significant coronary artery disease. It is additive to the previously accepted variables, and with regard to patient selection for further investigations it may help in the identification of high risk patients who warrant early invasive study. Furthermore, in those in whom the conventional variables of exercise testing are of borderline value an increased diastolic response

Table 3 *Correlation between exercise electrocardiographic (ECG) variables and coronary angiography. Figures are numbers of patients*

Exercise test variables	*Coronary angiography*				*Total*
	3VD and LM	*2VD*	*1VD*	*NCA*	
Normal diastolic blood pressure and:					
Positive ECG	7	12	2	6	27
Negative ECG	0	1	22*	11	34
Abnormal diastolic blood pressure and:					
Positive ECG	21	6	0	0	27
Negative ECG	8	3	0	0	11
Total	36	22	24	17	99

NCA, normal coronary artery.
*20 patients had previous infarction.

should alert the physician to the possibility of significant coronary disease. The role of the diastolic blood pressure response in other diseases and its modification by interventions such as surgery merit further study, for if it reflects significant left ventricular dysfunction it could be a valuable prognostic marker.

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Limitations of radionuclide ventriculography in the non-invasive diagnosis of coronary artery disease

A correlation with right heart haemodynamic values during exercise

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SUMMARY A consecutive series of 56 patients with chest pain but no evidence of previous myocardial infarction was prospectively studied by radionuclide ventriculography to determine the value of global and regional radionuclide indices in detecting coronary artery disease. The results were correlated with the clinical judgment of chest pain, the results of the exercise electrocardiogram, and the right heart haemodynamic measurements during exercise. As a result of the criteria for entry, the study group was representative of the population seen in such a clinical setting. Only 25% of patients had coronary artery disease. The predictive power of radionuclide ventriculography was limited. The conventionally used criterion that normal subjects have an increase in left ventricular ejection fraction of at least 5% with exercise provided only 78% sensitivity and 57% specificity. Fourier analysis and visual interpretation of radionuclide studies wrongly diagnosed three out of 10 patients with extensive disease requiring surgery.

These results suggest that radionuclide ventriculography is of limited value in the non-invasive diagnosis of coronary artery disease.

The recent development of radionuclide ventriculography offers a non-invasive method of assessing global and regional left ventricular function. Early studies[1-3] suggested that this method might be an almost perfect screening procedure for coronary artery disease, while recent reports have raised serious doubts.[4-7] Controversy continues to exist concerning the reliability of radionuclide ventriculography as a test for coronary artery disease before coronary angiography. Some previous studies are of limited value in this regard, because patients with a history of myocardial infarction were included, medications were not withdrawn before exercise stress testing, or healthy asymptomatic volunteers were used as control groups.

Avoiding these potential shortcomings, this prospective investigation was performed (*a*) to determine the ability of radionuclide ventriculography to identify those subjects with significant coronary artery stenoses within a consecutive series of patients with chest pain and (*b*) to assess the extent to which additional diagnositic accuracy is gained with the use of global and regional radionuclide indices compared with the history, the exercise electrocardiogram, and the evaluation of right heart haemodynamics during exercise.

Patients and methods

STUDY POPULATION

The study population consisted of consecutive patients admitted for the evaluation of chest pain

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which their referring doctor considered might suggest coronary artery disease. Patient selection was prospective and based on the history, physical examination, resting electrocardiogram, pulmonary function test, and chest radiograph. With the exceptions noted below, the series included all patients referred between 1 September 1982 and 30 June 1983 who met the following criteria: age 30–65 years; no evidence of previous myocardial infarction defined as a hospital diagnosis of infarction or the presence of significant Q waves on the resting electrocardiogram; no evidence of congestive heart failure or valvar heart disease; no arterial hypertension; normal standard chest radiographs; regular sinus rhythm; stable angina allowing the withdrawal of all medications except for short acting nitrates one week before exercise stress testing; normal routine pulmonary function test; and no previous coronary angiography or bypass graft surgery. Exercise stress testing and coronary angiography were carried out within two months (35 (19) days) of each other without an episode or change in the resting electrocardiogram suggesting an intervening coronary event. Informed written consent was obtained.

CLINICAL CLASSIFICATION OF CHEST PAIN

Patients were classified on the basis of their presenting symptoms at the time of admission before exercise testing[8] as having *(a)* typical angina if substernal chest discomfort precipitated by exercise and relieved by rest or glyceryl trinitrate within 10 minutes was present; *(b)* atypical angina if only two of the above features were present; or *(c)* non-anginal chest pain if only one or none of the above features was present.

RADIONUCLIDE AND HAEMODYNAMIC DATA ACQUISITION

Patients were instructed to stop taking all medications one week before the study. They were allowed to take only sublingual glyceryl trinitrate as necessary up until six hours before stress testing. They were familiar with supine bicycle exercise testing from a previous practice run.[9] Two hours before the radionuclide study supine exercise was carried out with an electrically braked bicycle ergometer to determine the maximum workload. The initial workload was 25 W, which was increased by 25 W increments every minute until a symptom limited maximum (chest pain, shortness of breath, fatigue) was reached. A six lead electrocardiogram (I, III, aVF, V4–6), blood pressure, and symptoms were recorded at rest and at one minute intervals during exercise. The ST segment response was considered to be positive if at least 1 mm flat or downsloping ST depression persisted 0·08 s after the J point in three consecutive cardiac cycles immediately after stopping exercise. The electrocardiogram was considered to be non-diagnostic in patients with bundle branch block.

In the nuclear imaging laboratory a flow guided open ended catheter (Flexo-Pulmocath (Grandjean), Intra Co, Saarbruecken, West Germany) was inserted into an antecubital vein and advanced into the pulmonary artery. Its position was verified by continuous pressure monitoring. Pressures were measured with a P23 Statham strain gauge from a reference level 5 cm below the sternal angle. They were averaged over 10 cardiac cycles at rest and during the fourth minute of the maximum workload. Electrocardiogram gated blood pool imaging of the heart was performed after in vivo labelling of red blood cells with 20 mCi (740 MBq) of technetium-99m. Patients were imaged in the left anterior oblique position which provided optimal ventricular separation on the storage oscilloscope. The scintillation camera was tilted to an angle of 15° caudally. This standard scintillation camera (LEM Scintillation Camera, Siemens Inc, Munich, West Germany) was equipped with a high sensitivity all purpose parallel hole collimator interfaced to a dedicated medical computer system (Digital Equipment Corporation, Maynard, Mass, USA). The image data were acquired in frame mode with 32 frames spanning the cardiac cycle. They were formatted into a 32×32 matrix. The pixel area was 6×6 mm^2. On completion of the resting study supine bicycle exercise was carried out as described above. Patient movement was minimised by the use of handgrips, shoulder restraints, and foam wedges. When the previously determined maximum workload was reached the patient was asked to continue exercising. Imaging started two minutes after the maximum workload was begun to ensure a relative steady state and continued until approximately 100 000 counts per frame were obtained (2–3 minutes). The occurrence of exercise induced pain suggesting angina was noted.

LEFT HEART CATHETERISATION

Each patient underwent biplane radio-opaque ventriculography in the 30° right anterior oblique and the 60° left anterior oblique position. Selective coronary angiograms were obtained in multiple projections by Judkins's method. Coronary artery disease was diagnosed if at least one major coronary artery had a lesion occluding >75% of the lumen.[10] The angiograms were interpreted by three observers. Disagreements were resolved by joint discussion.

RADIONUCLIDE DATA PROCESSING

The left ventricular ejection fraction was determined from the background corrected time-activity curve as previously described.[11] Briefly, the left ventricular regions of interest were manually outlined on the end systolic and end diastolic frames. Background activity was derived from a crescent shaped region adjacent to

Table 1 *Clinical characteristics and angiographic data in 56 consecutive patients evaluated for chest pain. Figures are numbers of patients unless stated otherwise*

	Normal coronary angiogram (n=42)	*Coronary artery disease (n=14)*
Mean (SD) age (yr)	49 (7)	49 (7)
Male	29	12
Female	13	2
History of:		
Typical angina	9	10
Atypical angina	16	2
Non-anginal chest pain	17	2
Coronary anatomy:		
Normal	42	0
One vessel disease	0	4
Two vessel disease	0	4
Three vessel disease	0	6
Subsequent operation	0	10

the inferolateral border of the end diastolic left ventricular outline. For the assessment of regional wall motion the left ventricular end diastolic cavitary silhouette was divided into eight segments by axes passing through its geometric centre at 45° to each other. The phase and the amplitude of the first Fourier coefficient were determined for each segment using a normalising procedure which set the mean left ventricular amplitude of each study at unity.[12] The standard deviation of phases was calculated for each study. This value was regarded as an index of synchronicity of left ventricular wall motion. It provides a diagnostic accuracy equivalent to that obtained with the use of phase distribution histograms of the individual left ventricular pixels. Finally, each study was visually assessed in an endless loop cine format by two experienced observers who were unaware of any clinical or angiographic data and was classified as normal or abnormal. No borderline category was permitted. An image was considered to be abnormal if regional wall motion abnormalities appeared or increased in severity during exercise. In the case of disagreement the image was re-examined and a consensus obtained. Patients with bundle branch block were excluded from the visual interpretation and the Fourier analysis.

STATISTICS

Values are expressed as mean (1 standard deviation). Only non-parametric procedures were used since some of the characteristics had non-Gaussian distributions. Individual changes in measurements from rest to exercise were compared by the Wilcoxon matched pairs signed rank test. The Mann-Whitney test was used for analysing intergroup differences. The beta function was used to illustrate the frequency distributions of the left ventricular ejection fractions.[13]

Results

PATIENT CHARACTERISTICS

Seventy three patients met the criteria for entering the study. Of these, 17 were excluded from the analysis: five patients refused coronary angiography; one had an acute myocardial infarction before angiography; in three the pulmonary artery pressures during exercise could not be determined; one had a psychoneurotic disorder; in four radio-opaque ventriculography showed a clinically unrecognised dilative cardiomyopathy; and in three the radionuclide study was technically inadequate. Table 1 summarises the clinical and angiographic data of the remaining 56 patients, only 25% of whom had angiographic evidence of coronary artery disease. Compared with the 42 patients with normal coronary angiograms those with coronary artery disease had a sex distribution consistent with a higher prevalence of coronary artery disease.

RIGHT HEART HAEMODYNAMICS

Table 2 shows the haemodynamic data. The resting diastolic pulmonary artery pressures were consistently within normal limits in both groups. The exercise induced increase was greater in the group with coronary artery disease ($p<0{\cdot}01$).

A level of 25 mm Hg, which is similar to the upper

Table 2 *Radionuclide and haemodynamic findings at rest and during maximum exercise stress testing in patients with and without coronary artery disease (CAD). Values are mean (SD)*

	Without CAD (n=42)	*With CAD (n=14)*
At rest:		
Diastolic pulmonary artery pressure (mm Hg)	9 (3)	9 (3)
Left ventricular ejection fraction (%)	63 (6)	62 (6)
Standard deviation of phases (°)	5·9 (2·3)	6·4 (2·6)
During exercise:		
Diastolic pulmonary artery pressure (mm Hg)	24 (7)	30 (9)
Left ventricular ejection fraction (%)	68 (10)	53 (14)
Standard deviation of phases (°)	6·2 (2·8)	12·1 (8·1)
Heart rate (beats/min)	140 (16)	132 (16)
Rate-pressure product (beats/min × mm Hg × 10^{-3})	27 (5)	24 (5)
Exercise tolerance (W)	140 (40)	110 (30)

Table 3 *Sensitivity, specificity, and predictive accuracy of clinical, electrocardiographic, haemodynamic and radionuclide findings. Values are percentages*

Test	*Sensitivity*	*Specificity*	*PA(+)*	*PA(−)*
Clinical assessment of chest pain*	86	40	32	89
Exercise electrocardiography†‡	71	79	55	88
Right heart haemodynamics†	78	59	39	89
<5% increase in LVEF	78	57	38	89
Fourier analysis of regional wall motion‡	64	84	60	86
Visual interpretation of radionuclide studies‡	57	95	80	86

*Typical or atypical angina *vs* non-anginal chest pain.

†A diastolic pulmonary pressure of >25 mm Hg and an ST segment depression of at least 1 mm are required for test positivity.

‡Patients with bundle branch block are excluded.

LVEF, left ventricular ejection fraction; PA(+), predictive accuracy of a positive result; PA(−), predictive accuracy of a negative result.

limit of normal during exercise in healthy men aged 61–83 years,[14] has been used in this laboratory to discriminate between positive and negative test responses. In this study this threshold value was diagnostically more accurate than a level of 20 mm Hg. Forty one per cent of the subjects with normal angiograms had pressures exceeding the normal range.

ELECTROCARDIOGRAPHY

The electrocardiogram was non-diagnostic in four patients, none of whom had coronary artery disease. Ten subjects failed to achieve at least 85% of their age related maximum heart rates without showing a significant ST depression and thus had unreliable though negative electrocardiograms. One of them was referred for coronary artery bypass surgery.

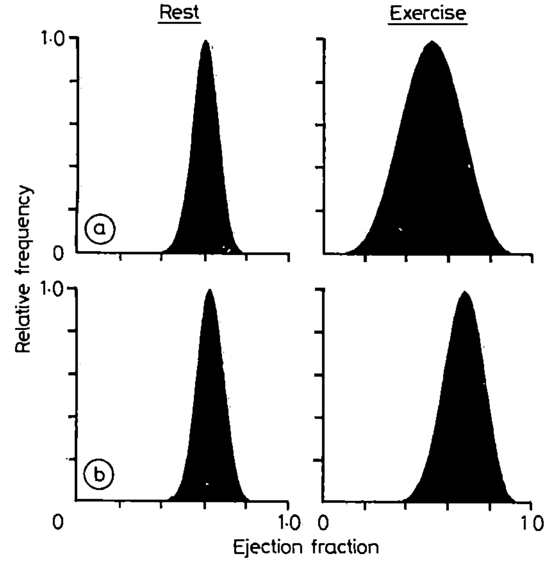

Figure *Frequency distribution curves of the left ventricular ejection fractions as evaluated by the beta function in patients (a) with and (b) without coronary artery disease during rest and exercise.*

CLINICAL ASSESSMENT OF CHEST PAIN

The predictive accuracy of the clinical assessment of chest pain compared favourably with that provided by non-invasive testing (Table 3). Typical angina, used as a separate criterion, yielded 71% sensitivity and 78% specificity. Although exertional chest pain was a feature of the history in most patients only 14% of those without but 78% of those with coronary artery disease had chest pain suggesting angina during exercise stress testing.

RADIONUCLIDE FINDINGS

As shown in the Figure the frequency distribution of the resting left ventricular ejection fraction was not significantly different in patients with and without coronary artery disease. The mean left ventricular ejection fraction increased from rest to exercise in the group with normal coronary angiograms. The group with coronary artery disease had a mean decrease in left ventricular ejection fraction during exercise. The individual variation was large.

The values for the standard deviation of phases, which are shown in Table 2, showed a tendency to increase with exercise in the group with normal angiograms ($p<0\cdot05$). The upper limits of normal were calculated from these values as the mean plus two standard deviations.[11] They were 10·5° at rest and 11·8° during exercise. If the latter was used as the diagnostic criterion only 43% of the group with coronary artery disease showed an abnormal phase distribution with exercise. All these patients were classified as having typical angina and experienced chest pain characteristic of angina during exercise stress testing. Phase analysis failed to detect coronary artery disease in any of the group with coronary artery disease who had atypical angina or non-anginal chest pain according to the clinical classification even if the threshold value for test positivity was lowered to the mean plus one standard deviation.

The lower limit of a normal amplitude during exercise was calculated for each segment from the patients with normal coronary angiograms as the mean relative amplitude minus two standard deviations. An abnormal left ventricular amplitude distribution was considered to be present if at least one myocardial segment showed an amplitude below this threshold level. The presence of an abnormal amplitude pattern during exercise proved to be more sensitive (57% *vs* 43%) but less specific (89% *vs* 95%) for coronary artery disease than an abnormal phase distribution. If an abnormal phase distribution or at least one abnormal segmental Fourier amplitude is regarded as indicating coronary artery disease the specificity is reduced to 84% and the sensitivity increased to 64% (Table 3). No significant additional diagnostic accuracy was obtained with the Fourier analysis compared with the visual interpretation by two experienced observers. The last approach yielded a fairly high specificity (95%) but proved to be insensitive (57%) in detecting coronary artery disease. The diagnostic accuracy of the conventionally used criterion that normal subjects have a $\geqslant$5% increase in left ventricular ejection fraction during exercise was almost identical to that of the evaluation of right heart haemodynamics during exercise.

SEX DIFFERENCES

Only two women had coronary artery disease. In the remaining 13 women the haemodynamic and radionuclide responses to exercise were not significantly different from those of the men with normal coronary angiograms.

Discussion

The results of this study reflect wide variations in the left ventricular ejection fraction during exercise in patients with coronary artery disease. This fact, which confirms the findings of Gibbons *et al*,[5] should not be surprising since a multitude of factors will interrelate to determine this complex variable. The resulting poor predictive power of the ejection fraction response to exercise indicates that the assessment of global left ventricular function cannot be relied on to predict the presence of coronary artery disease with acceptable accuracy. The Fourier analysis, as introduced by Geffers *et al*,[15] offers a means of objectively evaluating the regions of dyskinesia, which are considered to be a distinguishing feature of coronary artery disease.[16 17] The left ventricular phase distribution with exercise was recently suggested to be a highly sensitive and specific marker of regional myocardial ischaemia that was slightly superior to the visual interpretation of regional wall motion.[11] In this study, however, Fourier analysis as well as visual interpretation failed to detect coronary artery disease in three out of 10 patients who were referred for coronary artery bypass surgery on the basis of their angiographic findings. Two of these subjects were classified as having typical angina and had positive exercise electrocardiograms. One patient had two vessel disease with a 90% stenosis of the left circumflex artery and an occlusion of the right coronary artery with poor retrograde filling from the left circumflex artery. This patient had no significant increase in left ventricular ejection fraction and normal pulmonary artery pressures during exercise. The second patient also had two vessel disease with an 80% stenosis of the left anterior descending artery and an occlusion of the right coronary artery with poor retrograde filling from the left anterior descending artery. This patient had a normal ejection fraction response but raised pulmonary artery pressures during exercise. The third patient had an occlusion of the left anterior descending artery with fair retrograde filling from the right coronary artery. This patient had an entirely normal ejection fraction and pulmonary artery pressure response to exercise but failed to achieve 85% of the maximum predicted heart rate owing to severe angina without showing significant ST segment depression. Thus radionuclide ventriculography falls short of the demands for sensitivity that a screening test for coronary artery disease should satisfy. This finding requires careful scrutiny since it is at variance with a large number of previous reports.[1-3]

In our study exercise was performed supine. It is well known that there are important physiological differences in the results of supine and upright exercise tests. Upright and supine radionuclide studies are, however, equally effective in detecting coronary artery disease.[18 19] Patients were encouraged to exercise to a maximum. Patient movement and gating artefacts at maximum workload may produce less accurate radionuclide measurements. For optimum sensitivity, however, exercise stress testing must be carried out to maximum effort. A submaximal test may miss up to 50% of the ischaemic responses that could be elicited by performing the test to maximum effort.[20] The radionuclide studies were technically adequate in all patients included in the final analysis. Previous reports indicate that a standardised exercise protocol for radionuclide ventriculography does not exist. To prevent non-cardiac symptoms such as muscle weakness or internal heat burden from terminating exercise we used an exercise protocol with stages of only one minute in duration. A similar protocol was used by Christopher *et al.*[21] We conclude that a relative circulatory steady state did exist during radionuclide data acquisition at maximum workload since no significant change occurred in heart rate, blood pressure, or pulmonary artery pressure from the start of image collection until its end.

Stress testing does not detect anatomical lesions but reflects exercise induced abnormalities that are usually linked to an imbalance of oxygen supply and demand. A decrease in ejection fraction or an increase in the filling pressures may indicate functional impairment, but they are not specific for angiographically visible coronary artery disease. A normal angiogram does not necessarily imply normal function and vice versa. Thaulow *et al* found an abnormal ejection fraction response to exercise in a significant number of patients with normal coronary angiograms and anginal chest pain or positive exercise electrocardiograms.[22] They presumed that the abnormal radionuclide findings reflected heart muscle disease at an early stage. We suppose that many of our patients with patent vessels probably also had unidentifiable cardiac disease associated with abnormal function. This population was therefore considerably different from groups of healthy asymptomatic volunteers who are frequently studied to establish the range of the normal response to exercise.[1 23 24] The application of diagnostic criteria derived under such biased conditions to the routine patient with chest pain will inevitably be misleading. These criteria have to be defined and validated in a study group that is representative of the population encountered in such a clinical setting. Though five subjects who refused coronary angiography had to be excluded, we are convinced that the remaining patients were representative in terms of prevalence, symptoms, age, and sex distribution of those seen in a major diagnostic centre. A pretest or post-test referral bias[7] was avoided. We proceeded to angiography in each patient regardless of whether or not the non-invasive tests were positive. We presume that the fulfilment of this prerequisite for an accurate evaluation of test sensitivity and specificity[25] was a major reason why radionuclide ventriculography was found to be less reliable than previously reported. Numerous reports have included patients with a history of myocardial infarction,[11 23 26] which improves the sensitivity values. The rationale for excluding these subjects was that we considered it invalid to apply a test for determining whether or not coronary artery disease is present to a patient with documented coronary artery disease.

Except for short acting nitrates all medications were withdrawn one week before stress testing to ensure complete recovery from the effects of any cardioactive agent. Previous work has suggested that beta blockade improves exercise induced global and regional left ventricular dysfunction in subjects with coronary artery disease.[27] Battler *et al* reported a mean increase in exercise left ventricular ejection fraction of 22% with propranolol above that during the same exercise test without beta blockade.[28] Jones *et al* found that excluding patients receiving propranolol from the study group produced a considerable increase in sensitivity.[29] These data show that the results of studies that include patients receiving beta adrenergic blockade[6 11 30] are of questionable value. The relatively high sensitivity and specificity of the clinical assessment of chest pain in our study agree with those reported by others.[31 32] The limited predictive power of the ST segment response to exercise is also consistent with previous findings.[33 34]

The increase in the left ventricular diastolic pressure with exercise has been well documented in patients with coronary artery disease.[35–37] In the absence of clinical, laboratory, and radiological evidence of pulmonary or mitral valve disease the pulmonary artery diastolic pressure was used to reflect the left ventricular filling pressure.[14 38 39] Our findings indicate that the diagnosis of coronary artery disease cannot be excluded even if the threshold value for the positivity of the diastolic pulmonary artery pressure measurement is lowered to only 20 mm Hg. Two patients who were referred for bypass surgery would not have been diagnosed as having coronary artery disease if the assessment of right heart haemodynamics had been the criterion for proceeding to angiography. The disturbingly low specificity of this procedure is a serious limitation to its use as a screening method for coronary artery disease. Why many of our patients with normal coronary angiograms had a pronounced increase in diastolic pulmonary artery pressure to clearly abnormal values is still unclear. A diminished left ventricular compliance secondary to arterial hypertension cannot account for this finding, since subjects with this problem were excluded from the study. This study was not designed to establish the reason for abnormal radionuclide and haemodynamic responses to exercise in patients with normal angiograms. The responses do indicate, however, that the group of patients with normal coronary angiograms probably included a considerable number of patients with non-coronary heart disease. Such a group should therefore not be referred to as normal.

Our findings show that a direct move from clinical judgment to angiography is mandatory in patients classified as having typical angina, since non-invasive testing would only marginally alter the high pretest probability of coronary artery disease in these subjects. Bayes's theorem implies that screening procedures make their major diagnostic contribution when applied to the difficult group of patients with an intermediate level of disease prevalence.[40 41] In this study, however, the predictive power of all the screening procedures used was substantially limited. To compensate for this finding a combination of screening tests might be advocated. As a reflection of the relatively high false positive and false negative rates serial testing frequently provides contradictory results and thus does not appreciably modify the clinical estimate of disease prevalence.

Radionuclide ventriculography is valuable in assessing surgical and medical treatment. Because of our findings, however, we do not recommend its use in the non-invasive testing of patients with chest pain that might be of ischaemic origin. In the primary diagnosis of coronary artery disease this technique supplies little more information than that provided by the clinical judgment of chest pain.

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Indirect measurement of blood pressure during exercise testing can be misleading

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SUMMARY Indirect blood pressures recorded with a random zero sphygmomanometer were compared with simultaneous intra-arterial blood pressures recorded with the Oxford system. Twenty five patients undertook a graded bicycle exercise test, cycling at workloads increasing from 41, 65, 114, and 163 W (250 to 400, 700, and 1000 kpm per min) with each grade being maintained for three minutes unless the exercise test was terminated earlier at the point of fatigue. Intra-arterial pressures were recorded continuously and indirect measurements made at steady state levels in the 30 seconds before each change in grade and immediately after the termination of the exercise protocol. The mean difference in systolic blood pressure at 5·5 minutes of exercise showed that the indirect measurement underestimated the direct measurement. Immediately after the termination of exercise the blood pressure fell precipitiously to a highly significant degree. For both systolic and diastolic pressures there was considerably individual variability.

These data confirm that indirect methods of blood pressure measurement during dynamic exercise testing are inaccurate and may provide misleading information.

Blood pressure is a continuous physiological variable, with considerable changes from beat to beat and minute to minute in response to numerous influences both external and internal to the individual. Single recordings using the indirect technique (mercury in glass manometer, arm cuff, and Korotkoff sounds) can provide only a rough estimate of the true values, although the degree of accuracy can be improved by taking the mean of repeated measurements.[1 2] Comparisons of direct and indirect techniques[3–6] have shown that considerable discrepancies can occur even when recording conditions are ideal. Indirect measurements in the exercising subject are likely to be even more inaccurate because of the movement of the subject, the high level of extraneous noise, and the likelihood of increased variability induced by the increasing respiratory effort, yet most of the available information on the blood pressure response during exercise has been collected in this way.[7–9] Some workers[7 9 10] have attempted to improve their accuracy by recording the blood pressure immediately after the cessation of exercise, but intra-arterial recording has shown that the blood pressure falls very rapidly at this time and may return to the baseline levels within 30 seconds (Fig. 1).[11 12]

We report here the results of a formal comparison of direct and indirect recordings obtained at different grades of exercise and in the immediate postexercise period.

Patients and methods

Twenty five patients were recruited from the Harrow Hypertension Clinic; 11 were taking no medication and 14 were receiving antihypertensive treatment (10 patients were taking beta adrenoceptor blockers, of whom three were also taking prazosin, while the remaining four patients were taking prazosin alone). The group consisted of 19 men and six women with a mean age of 49 (range 23–66) years. All patients had a

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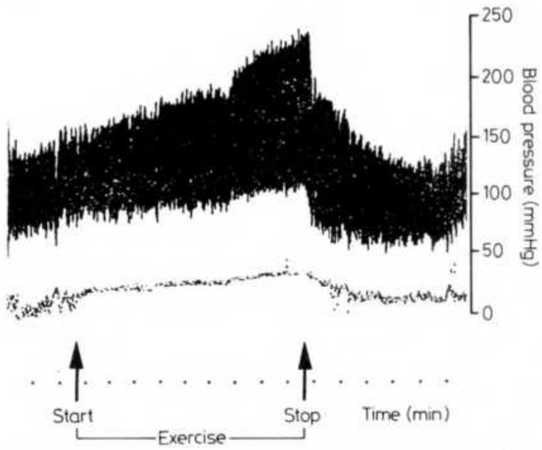

Fig. 1 *Intra-arterial recording of one patient during bicycle exercise testing.*

diagnosis of essential hypertension, having undergone routine testing to exclude secondary causes.

BLOOD PRESSURE RECORDING

Since indirect blood pressure was recorded from the dominant arm and direct pressure from the non-dominant arm the pressures in the two arms were assessed independently by two observers using a random zero manometer attached by a Y tube to two cuffs. The cuffs were then interchanged and further measurements taken. The procedure was then repeated with the observers changing arms. The relation of arm circumference was also assessed and found not to influence the data (manuscript in preparation).

Each subject then underwent intra-arterial ambulatory blood pressure monitoring, a technique which has been fully described and evaluated elsewhere.[13-15] Patients attended hospital in the morning, before 1100, for percutaneous insertion of the intra-arterial cannula into the brachial artery of the non-dominant arm. The blood pressure signal was measured with the Stott transducer-perfusion system and recorded on a Medilog I tape recorder (Oxford Medical Systems). This system has previously been validated and found to have a frequency response flat to 8 Hz,[14] as well as being accurate in comparison with a Millar tipped catheter at varying heart rate.[15]

EXERCISE TEST

After insertion of the cannula, each patient undertook a bicycle exercise test using an Elema (type 369) bicycle. They were requested to cycle at workloads increasing from 40·8, 65·2, 114, and 163 W (250, 400, 700, and 1000 kpm per min), each grade being maintained for three minutes or terminated earlier at the point of fatigue. The tests were carried out under standardised conditions with a constant laboratory temperature and at approximately the same time in the morning. Indirect blood pressures were recorded by one of two physicians in the last 30 seconds of each grade of exercise and immediately after exercise was stopped using a Hawksley random zero sphygmomanometer.[16] For diastolic measurements Korotkoff phase V was used. The exact time the pressure was recorded was marked on the intra-arterial tape using an electrical event marker.

The indirect pressure was recorded from the dominant arm of each patient, which was extended over the handle bars, and supported by the observing physician and was at the same level as the intra-arterial blood pressure transducer. The intra-arterial system was calibrated within 5 minutes of the exercise test.

DATA ANALYSIS

The tapes were replayed on a linear direct writing recorder (Watanabe) to check the signal quality and identify the event marks. A purpose built hybrid computer[17] was used to digitise a half minute mean blood pressure corresponding to each electrical event mark. It was not possible to identify the exact direct beats corresponding to the indirect systolic and diastolic pressures, so we used the mean blood pressure over the 30 seconds during which the indirect pressure was recorded. This has been shown to agree closely with single systolic and diastolic beats.[18] Figure 1 shows the rapid reduction of the blood pressure. In addition to this rapid fall in blood pressure there were fluctuations in pressure due to respiration, vasomotor activity, and other reflex activity. The only way this problem could be overcome would be to have an event made at the instants the cuff systolic and diastolic sounds were detected, so that a true beat by beat comparison could be made. Mistiming of the exact beat may lead to a significant error. We considered that the risk of mistiming estimating the exact beats was substantial and preferred the 30 second mean intra-arterial pressure.

The mean and standard deviation for each measurement were calculated as well as the mean difference (discrepancy) and the standard deviation and frequency distribution of between method differences, which were plotted in addition to a scatter plot.[19] Paired t tests were used to assess the mean differences between pairs of readings.

Numerous comparisons of resting indirect and direct arterial blood pressure measurements have been reported,[3-6] but it was not our intention to repeat this work. Resting indirect blood pressure measurements were not made routinely, but 12 patients did have resting indirect and direct arterial

Table 1 *Mean discrepancy values in blood pressure measured by indirect and direct methods during dynamic bicycle exercise*

Exercise time	*Recording method*	*Blood pressure (mm Hg)*							*Heart rate*	
		Mean	*SD*	*n*	*Mean difference between methods*	*SD of differences*	*t value*	*p value*	*Mean*	*SD*
					Systolic pressure					
Exercise (min)										
At 2·5	Indirect	181	29·4	25	−15	13·	·8	0·001	90	17·0
	Direct	196	33·6							
At 5·5	Indirect	188	36·5	25	−16	15·2	5·3	0·001	102	20·7
	Direct	204	38·3							
At 8·5	Indirect	200	35·1	13	−15	12·3	4·2	0·001	123	26·8
	Direct	215	36·9							
After	Indirect	200	37·8	25	−18	18·5	4·8	0·001	114	32·0
	Direct	217	41·4							
					Diastolic pressure					
Exercise (min):										
At 2·5	Indirect	114	19·6	25	4	14·1	1·2	0·2		
	Direct	110	17·2							
At 5·5	Indirect	111	21·0	25	−2	12·9	0·9	0·5		
	Direct	113	18·3							
At 8·5	Indirect	114	23·2	12	2	9·6	0·5	0·5		
	Direct	116	22·2							
After	Indirect	102	19·8	25	−14	15·4	4·7	0·0001		
	Direct	116	21·2							

blood pressures compared at a similar time to the above study. These data have been used to compare the mean difference between the two techniques of blood pressure measurement at rest and during exercise. Replicated (that is, repeated) resting mean differences were obtained and an analysis of variance undertaken from which a pooled estimate of the mean difference and standard deviation was obtained. This was used to compare the mean differences between indirect and direct at rest, after 2·5, 5·5, and 8·5 minutes of exercise, and on cessation of exercise.

The intersubject variability was tested by calculating the variance ratio (F test), and paired *t* tests were used to compare the mean differences of average resting clinic blood pressure and intra-arterial blood pressure with those after 2·5 and 5·5 minutes of exercise.

Results

No significant differences were found between the left and right arm blood pressures of these patients with a mean difference of <1 mm Hg and standard errors of 0·69/0·45 mm Hg.

COMPARISON OF INDIRECT AND DIRECT BLOOD PRESSURE

Table 1 summarises the detailed results for 2·5, 5·5, and 8·5 minutes and postpeak exercise. Since these were similar, only plots for 2·5 minutes of exercise and postpeak exercise are included in Fig. 2 (the lines are the lines of identity). The overall trend was the same for each stage; indirect systolic pressures grossly underestimated intra-arterial pressure, but the diastolic pressures were similar with both techniques. For both systolic and diastolic pressures there was considerable individual variability.

COMPARISON OF CLINIC INTRA-ARTERIAL BLOOD PRESSURE DIFFERENCES AT REST AND DURING EXERCISE

The replicated readings of resting blood pressure differences between indirect and direct recordings were subjected to an analysis of variance. The mean differences and standard deviations were calculated for the 12 patients who had resting indirect and direct blood pressures (Table 2). Analysis of the intersubject variability at rest compared with exercise (Table 2) showed that the trend was towards wider differences and greater variability of the indirect method in relation to intra-arterial blood pressures during exercise compared with at rest.

Discussion

Despite the well known fluctuation of the blood pressure with exercise, measurement of rapidly changing blood pressure using the standard indirect technique has been subjected to only limited critical validation. Under conditions of quiet supine rest the indirect cuff method compared with intra-arterial pressure has shown a wide range of differences,$^{3-6}$ and this discrepancy might be expected to get worse when measurements are attempted during strenuous exercise. Apart from the obvious physical difficulties of recording

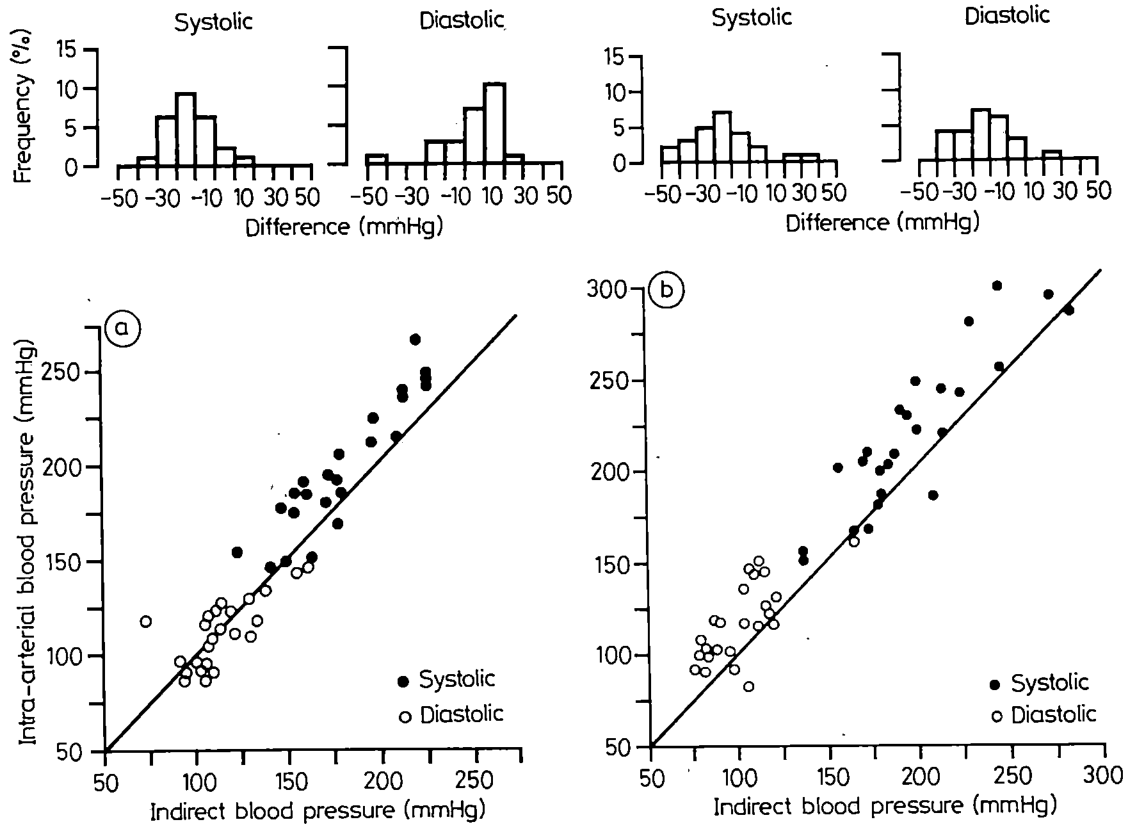

Fig. 2 *Scatter plot and frequency histograms comparing indirect and intra-arterial blood pressures (a) at 2·5 minutes of exercise and (b) immediately after the end of exercise (postpeak). (a) 28% of systolic and 44% of diastolic indirect blood pressures and (b) 24% of systolic and 36% of diastolic indirect blood pressures were within 10 mm Hg of the intra-arterial blood pressures recorded.*

indirect measurements during exercise, it is known that physiological changes in the cardiovascular system take place which may well affect the physical characteristics of the brachial artery and hence the intrinsic accuracy of the indirect technique.

The present study has confirmed the very rapid fall in blood pressure on cessation of exercise and has shown that during exercise the indirect systolic pressures consistently and significantly underestimate the intra-arterial pressures. The mean difference, ranging from 15 to 18 mm Hg, was slightly greater than previously reported in a similar comparison at rest when the mean difference was found to be 12 mm Hg.[19]

The mean discrepancy for diastolic pressures was

Table 2 *Analysis of blood pressure data recorded by indirect and direct methods at rest, at 2·5, 5·5, and 8·5 minutes of exercise, and after exercise*

Blood pressure	*Mean (SD) difference between methods*					*Statistical comparisons*									
	*Rest**	*2·5*	*5·5*	*8·5*	*Postpeak*	*2·5 vs rest*				*5·5 vs rest*				*Postpeak vs rest*	
						t†	p value	F‡	p value	t†	p value	F‡	p value	F‡	p value
Systolic	0·8 (12·2) (n=12)	−16·7 (15·1) (n=12)	−16·5 (18·8) (n=12)	−15·0 (14·0) (n=7)	−16·8 (12·3) (n=12)	3·13	0·01	1·52	0·50	2·46	0·03	2·36	0·17	1·02	0·98
Diastolic	−11·3 (9·0) (n=12)	2·4 (18·4) (n=12)	−4·8 (14·8) (n=12)	−5·8 (4·4) (n=6)	−15·7 (12·1) (n=12)	1·40	0·19	4·15	0·03	2·81	0·02	2·69	0·12	1·80	0·35

*From analysis of variance using two or three observations per subject.

†Paired t test comparing differences in blood pressure using indirect and direct methods.

‡Two sided-F test comparing intersubject variability in differences in blood pressure with two methods.

not as large as that for systolic pressures, individual differences ranging from −14 to +4 mm Hg. The indirect diastolic pressures were approximately the same on average as direct pressures at 2·5, 5·5, and 8·5 minutes of exercise, although there was considerable variation for individual subjects.

The large discrepancies (mean −18/−14 mm Hg) which were found in the postexercise period can be explained by the method of data collection. A single indirect pressure was recorded and compared with a 30 second mean intra-arterial pressure recorded while the indirect pressure was measured. Since intra-arterial pressures at the end of exercise fall rapidly this mean was taken on a downward pressure slope. Workers using the postexercise pressure with the indirect technique have the same problem, and it would seem to be impossible to measure the blood pressure using a sphygmomanometer at the same point of the slope for the same individual on different occasions or in different individuals at the same point of the falling pressure slope. Comparison of the indirect and intra-arterial blood pressure mean difference at rest and during exercise shows a trend to higher systolic mean differences during exercise, and the individual differences were more variable.

These data suggest that it is necessary to perform intra-arterial recordings during all exercise tests. For clinical purposes this is obviously impracticable, but we would advise caution in relying on such measurements. We recommend using intra-arterial recordings, for research purposes, where blood pressure measurements are important.

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Detection of high risk coronary artery disease by thallium imaging

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SUMMARY One hundred and three patients who underwent coronary arteriography were studied by thallium imaging and the results analysed by Bayesian principles to assess the usefulness of semi-quantitative stress thallium imaging for predicting the presence or absence of multivessel coronary disease. Significant disease was found in 80 patients, of whom 77 had abnormal thallium scans (sensitivity 96%). Thallium images were normal in 15 of 23 patients with no significant disease (specificity 65%). Multiple thallium segmental defects were found to be 90% sensitive and 65% specific for multivessel coronary artery disease and were present in 80% of patients with left main stem disease and in 93% of patients with triple vessel disease. A single thallium defect or normal scan excluded multivessel, left main, and triple vessel disease with 81%, 94%, and 91% predictive accuracy respectively. By Bayesian analysis the predictive accuracy for excluding multivessel disease was >90% in patients with a pretest probability of multivessel disease of ≤40%. Coronary arteriography to exclude multivessel disease is therefore unnecessary in a high proportion of patients with known or suspected coronary artery disease.

The Veterans' Administration[1] and European Coronary Surgery[2] studies have shown that aortocoronary bypass grafting can reduce the mortality in symptomatic patients with left main stem and triple vessel coronary artery disease and also in those with double vessel disease, which includes a long proximal left anterior descending artery lesion. The Coronary Artery Surgery Study confirmed the value of bypass grafting for left main disease even in minimally symptomatic or asymptomatic subjects.[3] As a result, coronary arteriography is frequently now performed expressly to define the likelihood of a patient's prognosis being improved by coronary surgery. It cannot, however, be performed in all patients with known or suspected coronary artery disease, and non-invasive methods to identify patients at high risk are needed.

Stress myocardial perfusion imaging with thallium-201 is known to be more accurate than exercise electrocardiography for predicting the presence and severity of coronary artery disease[4 5] and is also reported to predict accurately the presence of multivessel disease after myocardial infarction.[6 7]

We studied a population with chest pain or with known ischaemic heart disease who were referred for evaluation of the presence or severity of coronary artery disease. We sought to determine whether exercise testing and thallium imaging could predict the presence of multivessel disease, the prognosis for which can be improved by surgical revascularisation. Since the usefulness of any test depends on its predictive accuracy, which in turn depends not only on its sensitivity and specificity but also on the prevalence of disease in the population under study (Bayes's theorem),[8] we estimated the predictive accuracy of thallium imaging for different levels of disease prevalence.

Patients and methods

The study population comprised 103 patients who underwent stress testing and thallium scanning within 90 days of selective arteriography for the diagnosis or evaluation of coronary disease. There were 87 men

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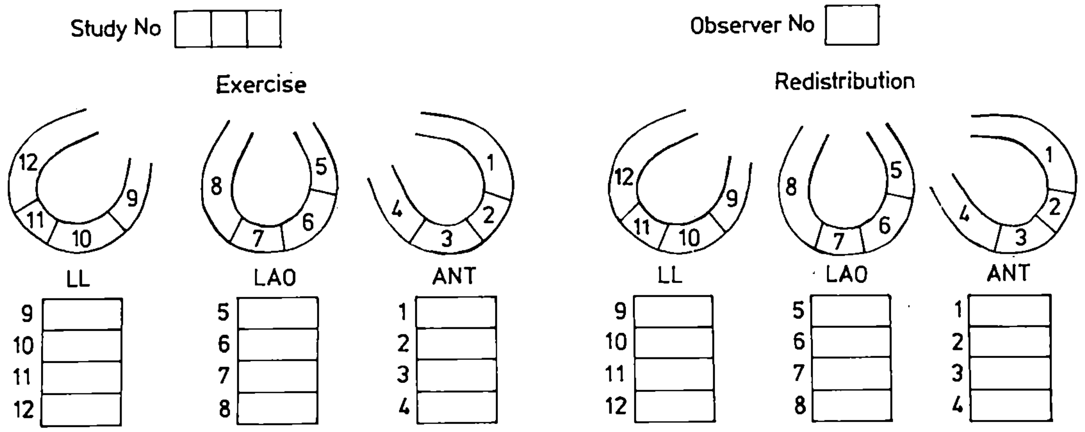

Fig. 1 *Diagrammatic representation of the exercise and redistribution myocardial perfusion images as used for reporting the thallium-201 scans.*

and 16 women with a mean age of 52·1 (range 35–72) years. Patients with valvar or congenital heart disease, cardiomyopathy, left bundle branch block, or a pacemaker in situ were excluded. Their drug treatment, which was the same at the time of both stress tests, consisted of beta blockers in 20, calcium ion antagonists in 12, long acting nitrates in eight, digoxin in four, and no treatment in 68.

Fifty four patients had a documented myocardial infarction or a pathological Q wave in the resting electrocardiogram or both.[9] The remainder had no evidence of previous infarction. Sixty six (64%, including 35 patients with myocardial infarction) had typical symptoms of angina.

EXERCISE ELECTROCARDIOGRAPHY

Treadmill tests with a symptomatic end point were carried out using a modified Chung protocol.[10] Two bipolar leads, CM5 (manubrium sterni negative, V5 position positive) and CC5 (right V5 position negative, V5 position positive), were used for electrocardiographic monitoring during and for five minutes after exercise. The electrocardiographic signal was analysed by a computer (CASE, Marquette Inc) which measured the ST segment level digitally. The mean ST segment level over a distance equal to one eighth of the RR interval (or 80 ms whichever was the less), the ST bar, was measured every 12 seconds and the digital values stored for recall at the end of the test. An abnormal ST segment response was defined as ST bar depression of 0·1 mV absolute and relative to the resting value.

THALLIUM SCINTIGRAPHY

A treadmill exercise protocol identical to that used for exercise electrocardiography was used for stress myocardial scintigraphy. At peak exercise 74 MBq of thallium-201 was injected via an indwelling venous cannula. Exercise was then continued for a further 30 seconds at a reduced workload. Within 5–10 minutes of the end of exercise imaging was performed using a Pho-Gamma II (Searle) scintillation camera with a high resolution collimator and a 20% window about the 80 KeV photo peak of thallium-201. Three hundred thousand counts were acquired in the anterior, 45° left anterior oblique, and left lateral

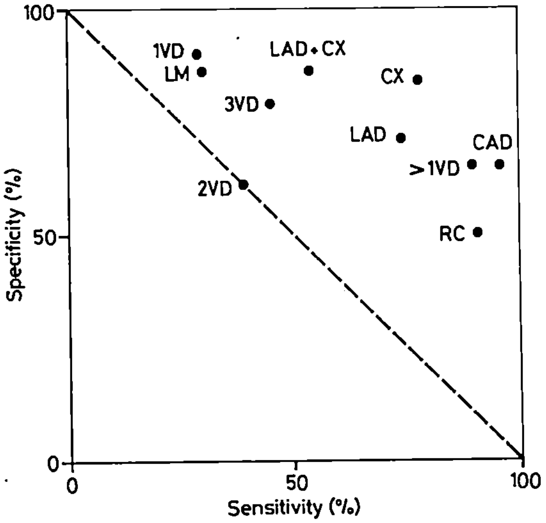

Fig. 2 *Relative values of sensitivity and specificity for the prediction of the presence, location, and number of diseased vessels by segmental analysis of thallium-201 images. 1VD, one vessel disease, 2VD, two vessel disease; >1VD, multivessel disease; LM, left main; LAD, left anterior descending; CX, circumflex; CAD, coronary artery disease; RC, right coronary.*

views. A lead sheet shielded the camera from activity due to the abdominal uptake of thallium. Redistribution scans were obtained in the same views 3–4 hours after exercise. The data were stored on hard disk in a 64×64 matrix and were analysed by a Gamma 11 computer (Digital Equipment Corp).

The exercise and redistribution scans were analysed semiquantitatively from the images displayed on the cathode ray tube by two experienced observers who were unaware of the results of other investigations. The images were interpolated to a 128×128 matrix, 30% of the lower threshold was subtracted, and nine point smoothing was carried out. A 15 point colour scale was used to identify areas with 25% count reduction relative to the myocardial area of maximal count density, and these areas were defined as abnormal. To detect redistribution of thallium the early and late scans were compared side by side.

To identify the location of perfusion defects the thallium images were divided into 12 segments and scored as shown in Fig. 1. The following myocardial segments were considered to be supplied by the individual major coronary vessels: left anterior descending, segments 1, 8, 12; circumflex, 5, 6, 9; and right coronary, 3, 4, 7, 10 (Fig. 1). Areas 2 and 11 were considered non-specific for any coronary vessel and the scans were reported so as to arrive at the least number of vessels that could account for the observed defects.

CORONARY ARTERIOGRAPHY

The right and left coronary arteries were selectively

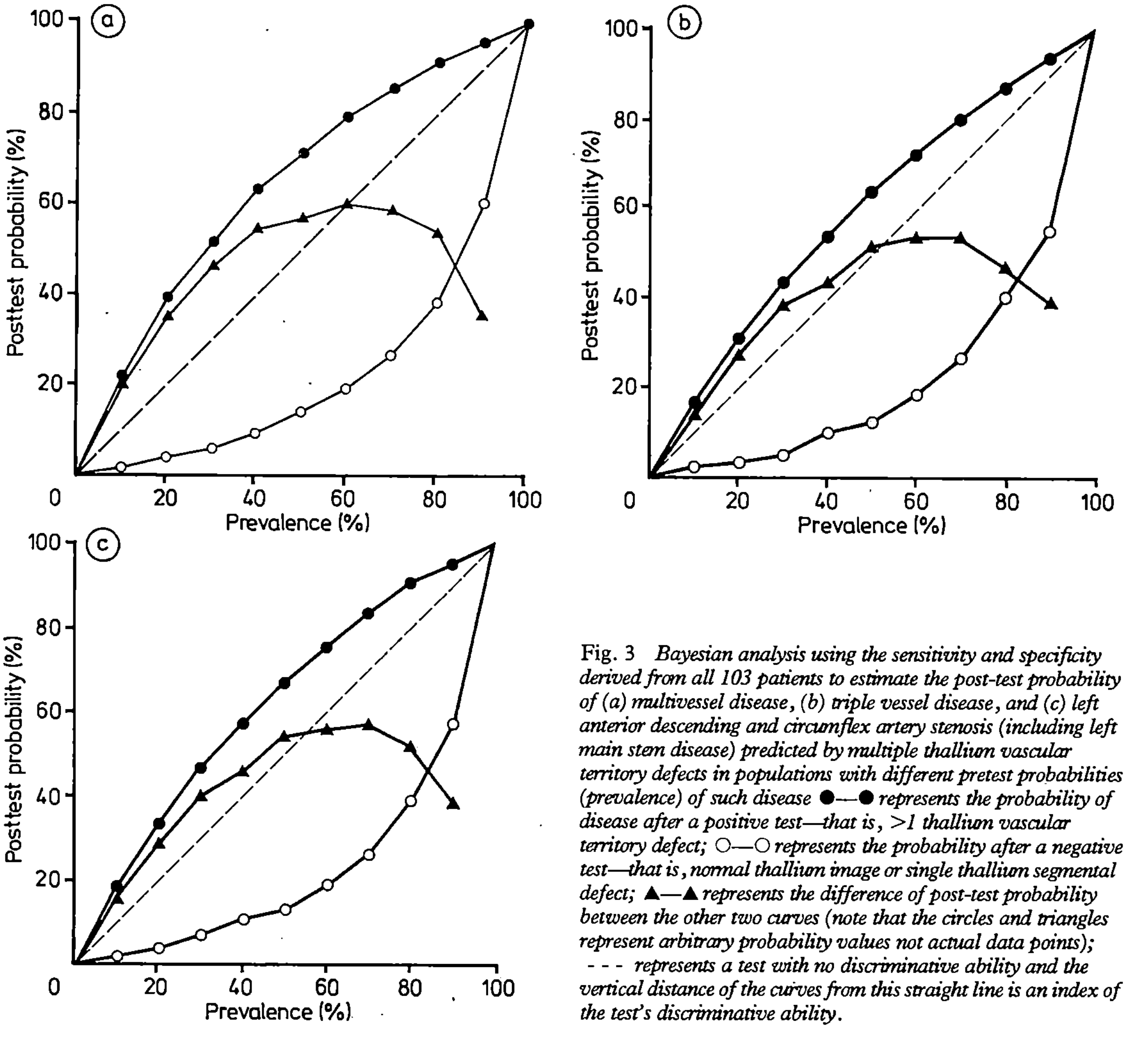

Fig. 3 *Bayesian analysis using the sensitivity and specificity derived from all 103 patients to estimate the post-test probability of (a) multivessel disease, (b) triple vessel disease, and (c) left anterior descending and circumflex artery stenosis (including left main stem disease) predicted by multiple thallium vascular territory defects in populations with different pretest probabilities (prevalence) of such disease ●—● represents the probability of disease after a positive test—that is, >1 thallium vascular territory defect; ○—○ represents the probability after a negative test—that is, normal thallium image or single thallium segmental defect; ▲—▲ represents the difference of post-test probability between the other two curves (note that the circles and triangles represent arbitrary probability values not actual data points); - - - represents a test with no discriminative ability and the vertical distance of the curves from this straight line is an index of the test's discriminative ability.*

Table 1 *Results of coronary arteriography in 103 patients. Figures are numbers of patients*

	Myocardial infarction	
	Absent (*n*=*49*)	*Present* (*n*=*54*)
No significant disease	23	0
Luminal stenosis >70%	26	54
No of diseased vessels:		
1	8	9
2	7	16
3	11	29
Location:		
Left anterior descending artery	22	45
Circumflex artery	17	44
Right coronary artery	16	37
Left main coronary artery and three vessel disease	1	8
Left main coronary artery alone	0	1
Left anterior descending and circumflex arteries	15	29

injected by Judkins's or Sones's technique. Significant disease was defined as ≥70% stenosis of a major coronary vessel or ≥50% stenosis in the case of the left main coronary artery. When significant disease was found in a dominant right coronary artery, the circumflex artery being rudimentary, or vice versa, two vessel disease was considered to be present. The arteriograms were reported independently by a radiologist and a cardiologist who conferred in cases of disagreement. The results of thallium imaging did not influence the decision to perform coronary arteriography.

ANALYSIS

The findings of thallium myocardial scintigraphy and stress electrocardiography were compared with the results of coronary angiography to determine the ability of the non-invasive tests to detect and identify the location of significant coronary artery disease. Sensitivity was defined as (true positives)/(true positives+false negatives) and specificity as (true negatives)/(true negatives+false positives). Positive predictive accuracy is the proportion of positive tests and negative predictive accuracy the proportion of negative tests that are correct.

The values of sensitivity and specificity within groups were compared by means of McNemar's matched pairs test. Between group comparisons of sensitivity, specificity, and predictive accuracy were performed by the probability of a proportion. Values of $p<0{\cdot}05$ were considered to be significant.

BAYESIAN ANALYSIS

To be of practical use to clinicians the probability of an individual patient having disease in the event of a positive and in the event of a negative test must be known. According to Bayes's theorem this post-test probability of disease depends on the pretest probability of disease as well as on the test's sensitivity and specificity.[8] The data from the Coronary Artery Surgery Study,[11] or other sources,[8] can be used to estimate the pretest probability of disease in a given patient if the age, sex, and type of symptoms are known. It was assumed that the test's sensitivity and specificity were independent of disease prevalence.[8] The post-test probability of disease can then be derived from the following equations:

(*a*) $P(+)=\dfrac{\text{Pre}}{\text{Pre}+(1-\text{Pre})/\text{L}}$ where P(+) is the post-test probability of disease when the test is positive; Pre, the pretest probability of disease; and L, the likelihood ratio (sensitivity/(1-specificity)).

(*b*) $P(-)=\dfrac{\text{Pre}}{\text{Pre}+(1-\text{Pre})\times \text{U}}$ where P(−) is the post-test probability of disease when the test is negative; and U, the unlikelihood ratio (specificity/(1-sensitivity)).

Using the values of sensitivity and specificity from this study P(+) and P(−) were calculated and plotted on a vertical axis with the pretest probability, range 0–100%, on the horizontal axis and the curves so obtained are shown in Fig. 2.

Results

CORONARY ARTERIOGRAPHY

Significant coronary narrowing was found in all the 54 patients with previous myocardial infarction and in 26 (53%) of those with no evidence of previous infarction. Six patients had luminal stenoses of <70%—five in three vessels and one in a single vessel—and 17 patients had no abnormality of the major coronary vessels. Table 1 shows the results of arteriography.

THALLIUM SCINTIGRAPHY

Figure 3 shows the sensitivity and specificity of thallium imaging for predicting the presence, location, and extent of coronary artery disease. With an ideal test for coronary disease all points would lie in the upper right hand corner of the graph. Of the 80 patients with significant coronary disease, 77 had at least one myocardial area of diminished (fixed or reversible) thallium uptake (sensitivity 96%). The thallium images were abnormal in all 54 patients with previous myocardial infarction: 17 had fixed defects only, 29 had both fixed and reversible defects, and eight had reversible defects only. The thallium scintigrams were abnormal in eight of the 23 patients with no significant coronary disease (specificity 65%) (Table 2), none of whom had a previous myocardial infarction. Five of these had normal coronary arteries and three had non-significant disease. In patients with no previous infarction thallium imaging had a sensitivity of 88%, a specificity of 65%, a positive predictive accuracy of 74%, and a negative predictive accuracy of 83%.

Redistribution of thallium between the early and late scans was seen in 55 patients with coronary disease. The proportion of those with infarction (37 of 54) and with no infarction (18 of 26) was the same (69%). Redistribution was seen in only three patients (with normal coronaries) out of 23 with no significant arteriographic disease (specificity 87%).

Prediction of individual coronary vessel disease

The sensitivity of segmental thallium uptake defects for detecting individual vessel disease was 91% for disease of the right coronary artery compared with 77% for the left anterior descending artery ($p<0{\cdot}05$) and 76% for the circumflex ($p<0{\cdot}05$ *vs* right coronary; NS *vs* left anterior descending) (Fig. 3). The specificity of segmental thallium defects was 88% for circumflex disease, 69% for the left anterior descending ($p<0{\cdot}05$), and 50% for the right coronary ($p<0{\cdot}01$ *vs* circumflex). The specificity of left anterior descending and right coronary defects did not differ significantly.

In patients with single vessel disease the values of sensitivity and specificity for each coronary vessel were: left anterior descending, 10/11 (91%) and 1/6 (17%); circumflex, 1/2 (50%) and 10/15 (67%); and right coronary, 3/4 (75%) and 3/13 (23%) respectively.

Prediction of the number of diseased vessels

Table 2 shows the numbers of patients having one, two, or three thallium vascular segmental defects and their arteriographic classification. A minority of patients in each arteriographic group was correctly classified by thallium imaging. As plotted in Fig. 3, the specificity of thallium prediction for one and three vessel disease was high, but for two vessel disease it had no useful predictive ability. Eight of the 10 patients with single vessel disease but multiple thallium segmental defects had <70% stenoses in at least one other major coronary vessel.

Left main stem disease

Nine of the 10 patients with left main coronary artery disease had triple vessel disease in addition. Three of these were correctly identified by thallium defects in three coronary vessel regions (sensitivity 30%, Fig. 3). A further three had defects in the territories of the left anterior descending and right coronary: one had circumflex and right coronary defects, one an isolated right coronary defect, and one a normal thallium scan. One patient with previous infarction had isolated left main stem disease and had thallium defects in the territories of the left anterior descending and right coronary arteries.

Fifty four patients had left main coronary artery disease or combined disease in the left anterior descending and circumflex arteries. Twenty nine of these had thallium uptake defects in the corresponding myocardial segments (sensitivity 54%). The specificity of combined left anterior descending and circumflex defects was 42/49 (86%). The positive and negative predictive accuracies were 81% and 63% respectively.

Multiple segmental thallium defects and multivessel disease

Using the criterion of thallium defects in more than one vascular territory the sensitivity for detecting high risk coronary disease was high, but the specificity was moderate (Table 3). Of 18 patients with normal thallium images, only one had multivessel (left main stem and triple vessel) disease—that is, the predictive accuracy of a normal scan for the absence of multivessel disease was 17/18 (94%).

EXERCISE ELECTROCARDIOGRAPHY

The sensitivity and specificity of 0·1 mV ST segment depression for detecting coronary artery disease in patients with no previous infarction were 18/26 (69%) and 15/23 (65%) respectively (both NS *vs* thallium imaging). The sensitivity of ST segment depression for the detection of multivessel disease was 62%, for three vessel disease 60%, and for left main disease 50%. Thus in this study two lead stress testing was no more sensitive for detecting serious multivessel disease than for detecting coronary artery disease in general.

Table 2 *Prediction of number of diseased coronary vessels by thallium imaging. Figures are numbers of patients*

	No of diseased vessels by thallium imaging				*Total*
	0	*1*	*2*	*3*	
No of diseased vessels by angiography:					
0*	15†	4	4	0	23
1	2	5†	8	2	17
2	0	3	9†	11	23
3	1	2	19	18†	40
Total	18	14	40	31	

*Includes six patients with non-significant disease (<70% luminal stenosis).
†Number of patients correctly classified by thallium-201 imaging.

Table 3 *Multivessel coronary disease prediction by thallium defects in more than one vessel's territory (n=103). Figures are numbers (%)*

	Sensitivity	*Specificity*	*Positive predictive accuracy*	*Negative predictive accuracy*
Left main disease	8/10 (80)	30/93 (32)	8/71 (11)	30/32 (94)
Left main disease or left anterior descending and circumflex artery disease	49/54 (91)	27/49 (55)	49/71 (69)	27/32 (84)
Three vessel disease	37/40 (93)	29/63 (46)	37/71 (55)	29/32 (91)
More than 1 vessel disease	57/63 (90)	26/40 (65)	57/71 (80)	26/32 (81)

Using the criterion of either an abnormal thallium image or an abnormal ST segment exercise response for a positive test the sensitivity for the detection of coronary artery disease was 88% (NS *vs* thallium and *vs* ST alone) but the specificity was 35% ($p<0\cdot05$). Defining an abnormal test as one in which both the thallium scan and the ST segment exercise response were abnormal gave a lower sensitivity (62%, $p<0\cdot05$, *vs* thallium alone), but the specificity increased to 96% ($p<0\cdot05$ *vs* thallium alone). Thus combined analysis yielded an improvement in specificity only at the cost of a loss of sensitivity, and in this study there was no significant improvement of predictive accuracy.

BAYESIAN ANALYSIS

When the criterion of multiple segmental thallium defects was used to construct curves relating pretest and posttest probabilities of high risk coronary artery disease (Fig. 2) a relatively low increment of probability of disease with a positive test was noted at all disease prevalence levels, which is in keeping with the low specificity. The value of a negative test for excluding multivessel disease was high owing to the test's high sensitivity. In populations with a pretest probability of high risk disease of $\leqslant 30\%$ a negative test reduced the post-test probability to $\leqslant 5\%$ for multivessel, left main, and triple vessel disease.

Discussion

While the value of aortocoronary bypass surgery for the relief of intractable angina is not disputed its effect on life expectancy in patients with coronary artery disease is more controversial.[1,2] The Veterans Administration[1] and European Coronary Surgery[2] studies have reported an improvement in prognosis in certain categories of patients treated surgically compared with controls. These categories were defined in terms of coronary anatomy, and, therefore, although we have to rely on the results of these two studies when deciding for or against coronary surgery, the non-invasive tests used to detect coronary artery disease must be compared with coronary arteriography. Exact agreement between the results of thallium imaging or stress electrocardiography and coronary arteriograpy is not to be expected since the non-invasive methods give functional as opposed to anatomical information about the myocardium. Both non-invasive methods probably have a prognostic value independent of the arteriographic findings.[13–15] We have evaluated the accuracy of planar thallium imaging for the detection or exclusion of multivessel disease, for which coronary bypass surgery is thought to improve the prognosis. We sought to determine whether coronary arteriography can be avoided in some patients and whether the addition of ST segment analysis can improve the accuracy of thallium imaging alone.

Stress thallium-201 scintigraphy has been shown to be more accurate than stress electrocardiography for detecting obstructive coronary artery disease.[4,5] We found semiquantitative thallium imaging to be highly sensitive (88% in patients with no previous infarction, 96% overall), a value which corresponds with the 82% average of studies cited by Okada *et al*,[4] which used subjective visual interpretation, and is comparable to the sensitivity reported with quantitative thallium image analysis.[16,17] The sensitivity of perfusion scintigraphy in this study was probably enhanced by the definition of significant coronary disease as $\geqslant 70\%$ luminal stenosis. Moderate (50–70%) stenoses are more frequently associated with a normal perfusion pattern.[17] Furthermore, there was a high prevalence of multivessel disease—63 of 80 (79%) patients—for which thallium imaging is more sensitive than for less extensive disease.[18]

The specificity of thallium imaging in this series (65%) is lower than in most reported studies. The choice of 70% stenosis as significant may have contributed to this. Three of the six patients who had coronary narrowing of <70% luminal diameter had abnormal thallium scans, which may indicate that these lesions were haemodynamically significant. Angiography frequently underestimates the true extent and severity of coronary disease and, in the range 25–70% stenosis, is subject to considerable interobserver variability.[19,20]

We found that disease of the right coronary artery was most readily detected (91%) followed by left anterior descending (77%) and circumflex disease (76%). Massie *et al* found similar values of sensitivity and concluded that the severity of vessel stenosis was the most important factor determining the sensitivity of thallium imaging for detecting individual vessel disease.[21] Maddahi and colleagues report that quantitative thallium analysis affords a small, but important, improvement in identifying diseased vessels, which may be valuable in evaluating the functional significance of coronary stensosis in the 50–70% range.[17] As noted by others, thallium imaging was a poor predictor of the number of diseased vessels,[21 22] and this may be due to the variability of coronary vessel dominance, especially in the inferior wall of the left ventricle.

The value of segmental analysis of thallium uptake for the prediction of multivessel coronary artery disease has been questioned.[21–25] Lenaers *et al* reported that 52% of patients with scintigrams suggesting single vessel disease had multivessel disease.[23] McKillop *et al* also concluded that semiquantitative thallium imaging could not help in identifying patients with high risk coronary disease who might benefit from surgery.[24] Maddahi *et al* reported that a higher proportion of coronary lesions in patients with triple vessel disease was detected by quantitative thallium imaging than by visual interpretation (83% *vs* 53%).[17] Gewirtz *et al* also reported an improved lesion detection rate with quantitative analysis, but the sensitivity for detecting patients with triple vessel disease was increased only from 33% to 48%.[26]

The sensitivity and specificity for detecting left main, triple vessel, and multivessel disease by corresponding segmental thallium defects in our study (Fig. 3) do not differ appreciably from those reported by others. Sensitivity for detecting high risk coronary artery disease was increased by using the criterion of multiple segmental defects. This results in a loss of specificity, but may be justified on the basis of the variability of predominance of the right and left coronary circulations and by our knowledge of the prognostic significance of multiple perfusion defects.[14 15]

The finding of multiple defects in 10 of our patients with single vessel disease implies that the stenoses of <70% in other vessels (in eight patients) were significant or that extensive myocardium was jeopardised by disease in one major coronary vessel (in two patients). Compared with a single defect or normal thallium scan, even in patients with angiographic single vessel disease, multiple thallium defects predict future cardiac events, both in patients presenting with chest pain[14] and after myocardial infarction.[15]

In this study three patients with triple vessel disease had either a normal thallium scan (one patient) or only one segmental defect (two patients). Diffusely decreased myocardial perfusion as occurs with severe three vessel disease can result in an image with homogeneously decreased thallium uptake but no identifiable defects.[23 24] Similarly, the finding of only one segmental defect in two patients with triple vessel disease may imply that only the area of greatest hypoperfusion was identified or that collaterals were preserving perfusion to other regions.

When multivessel disease coexists with myocardial infarction thallium imaging may be used to assess the presence of reversible ischaemia in the non-infarcted areas. Revascularisation of jeopardised myocardium may be very important in patients with previous infarction since preservation of left ventricular function may benefit their prognosis.[27]

According to Bayes's theorem the predictive value of an inaccurate test depends on the prevalence (or pretest likelihood) of disease in the population under study as well as on the test's sensitivity and specificity, and the latter were assumed in this study to be independent of disease prevalence. This assumption may be questioned, as thallium imaging might be more sensitive in a population with a high prevalence of coronary artery, and thus multivessel, disease.[18] The utility of our Bayesian approach can, however, be judged only by testing it prospectively in a new population of patients. When Greenberg and colleagues evaluated exercise testing in this way they found Bayesian analysis to be equally as accurate as discriminant function analysis[28] (which does not assume independence of test sensitivity and disease prevalence).

Inaccurate tests are of limited value in patients with a pretest likelihood of disease >90% or <10%. When the values of sensitivity and specificity obtained in this study were used to calculate the post-test probability of multivessel disease in populations with different pretest probabilities, we found that a negative test excluded multivessel coronary artery disease with >90% probability if the pretest probability of multivessel disease was <40% (see Fig. 2). Data from the Coronary Artery Surgery Study indicated that approximately half the patients with no previous infarction undergoing coronary arteriography fell into this category.[11] The pretest probability of left main or triple vessel disease was less than 40% in over 70% of patients undergoing coronary arteriography in this study.[11] Thus the need for arteriography as a guide to prognosis can be avoided in a high proportion of patients presenting for investigation of chest pain.

We used two bipolar leads, CM5 and CC5, a combination reported to be as sensitive and specific as multiple lead systems for detecting coronary artery disease.[29] In this study, however, the sensitivity and specificity of ST segment displacement during exercise were only 69% and 65% respectively in patients without previous myocardial infarction. The addition of ST segment analysis did not improve the predictive accuracy of thallium imaging.

The finding that in patients with a high prevalence of multivessel coronary artery disease high risk disease can be excluded with confidence by means of stress thallium imaging suggests that in a less selected population a normal thallium scan or single perfusion defect indicates the absence of multivessel disease and renders coronary angiography for prognostic purposes unnecessary.

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Is low energy intake a risk factor for ischaemic heart disease?

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SUMMARY The relation between total energy intake and the development of ischaemic heart disease was investigated from a review of all available data including the results of 26 years of follow up from a longitudinal study of diet and ischaemic heart disease. A consistent inverse relation was found, whose strength and consistency are similar to those of other established risk factors.

It is concluded that there may be a minimum energy intake below which the risk of ischaemic heart disease is increased.

The association of ischaemic heart disease mortality and dietary factors, between populations, was first identified more than 25 years ago[1] and subsequently confirmed by others.[2-4] Positive associations were found not only with the proportion of energy from both total and saturated fat but also with total energy intake.[5,6] Indeed it was postulated that excessive energy intake from all sources rather than from any one particular kind of food was associated with ischaemic heart disease.[7] A prospective study in the United Kingdom of groups of bankers and London busmen, however, suggested that a high energy intake may be protective against ischaemic heart disease.[8] We have subsequently examined available data from other diet-heart studies together with previously unpublished data from the UK study to determine whether this relation is consistent and to consider the possible explanations for such an association.

Review of the evidence

OBSERVATIONAL STUDIES BETWEEN POPULATIONS

The findings from observational ecological studies (Table 1) showed[2,4,5] that populations with a high ischaemic heart disease mortality are the affluent countries that also have high fat and energy levels available for consumption. The Seven Country study by Keys[9,10] using a diet methodology appropriate for characterising groups,[11] found no relation between ischaemic heart disease and energy intake, calculated as energy per kilogram body weight. They did, however, find that there was less disease in the communities with high physical activity, though the relation between physical activity and energy intake was not examined.

COMPARATIVE STUDIES OF RELATED POPULATIONS WITH DIFFERING RISKS

In a study comparing dietary habits in Boston men of Irish origin with those of their brothers remaining in Ireland[12,13] the Irish brothers had a mean daily energy intake of 500 cal_{th} (2·10 MJ) more than their Bostonian counterparts despite being about 10% smaller in weight and having half the mortality rate due to ischaemic heart disease. The Irish brothers were noted to take more exercise.

In an attempt to explain the lower standardised mortality rate of ischaemic heart disease in Iowa farmers compared with their town dwelling counterparts the ischaemic heart disease risk factors were compared in the two groups.[14] This showed that the farmers smoked less, exercised more frequently, and had a mean energy intake of 430 kcal_{th} (1·81 MJ) greater than the towns people. Conversely, the percentage fat intake was similar and the ratio of polyunsaturated to saturated fatty acids was lower in the farmers.

TIME TRENDS WITHIN POPULATIONS

Kahn observed that despite a fall of 10% in total energy intake in the United States in the first six

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Table 1 *Between population comparisons of ischaemic heart disease mortality and dietary fat and energy intake*

Study	*No of countries*	*Population (age range in yr)*	*Disease definition*	*Energy (r_s)**	*% Fat (r_s)**
Yerushalmy and Hilleboe[2]	22	Male (55–59)	ICD: B25–28	+0·64	+0·44
Jolliffe and Archer[4]	20	Male (55–59)	ICD: B26	+0·55	+0·73
Masironi[5]		Male (55–64)	AHD		
1940s and 1950s	25			+0·75	+0·63
1960s	38			+0·69	+0·74

*Food energy data derived from Food and Agricultural Organisation food balance sheets. r_s, Spearman's rank correlation coefficient. AHD, arteriosclerotic and degenerative heart disease; ICD, international classification of diseases.

decades of this century there has been an increase in ischaemic heart disease rates though little change in serum cholesterol concentrations.[15] Figure 1 shows similar data for the United Kingdom from 1960 to 1978 (that is, the period of the Eighth Revision of the International Classification of Diseases). There was an increase in age adjusted ischaemic heart disease mortality rate between 1960 and 1972 followed by a levelling off in both men and women.[16 17] During this period there was a steady decline in energy intake, which was particularly pronounced in 1970–74.[18] Statistically, for the 19 years, there are strong inverse correlations between this population estimate of energy intake and mortality in both men ($r = -0·78$) and women ($r = -0·69$).

RETROSPECTIVE STUDIES

In the International Atherosclerosis Project there was a trend of increasing coronary artery atheroma with a decrease in energy intake, though this was not statistically significant.[19] In a similar study of 226 men from the Honolulu Heart Study both energy and starch intake were significantly inversely related to the extent of coronary atheroma at necropsy.[20] A detailed case-control study in North Dakota, however, found no association between ischaemic heart disease and mean energy intake.[21 22]

PROSPECTIVE STUDIES

There have been several prospective studies involving dietary assessment. A part of the Western Collaborative Group study used a seven day diary method of dietary assessment.[23] A two and a half year follow up showed that 25 men who developed electrocardiographic changes of ischaemic heart disease had a lower initial energy intake compared with 80 disease free men (2100 *vs* 2280 kcal_{th} (8·82 *vs* 9·58 MJ)).

Not all prospective studies of diet and ischaemic heart disease have reported on total energy intake, though such data must have been collected. Thus there are no dietary data pertinent to this question either from the Albany[24] or the Minnesota[25] studies. We have found seven prospective population studies from which at least four years of follow up data are available. We grouped the studies into areas of high and low incidence of ischaemic heart disease because of the very different levels of energy intake found. The high incidence areas included Framingham,[26 27] Zutphen,[28] Western Electric (Chicago),[29 30] and UK bankers and busmen[8 31] and the low incidence areas Hawaii,[32] and the studies of both urban and rural populations in Puerto Rico.[33] The studies varied in their study population, the method of dietary inquiry, the outcome measures published, and the duration of follow up; Table 2 shows these differences.

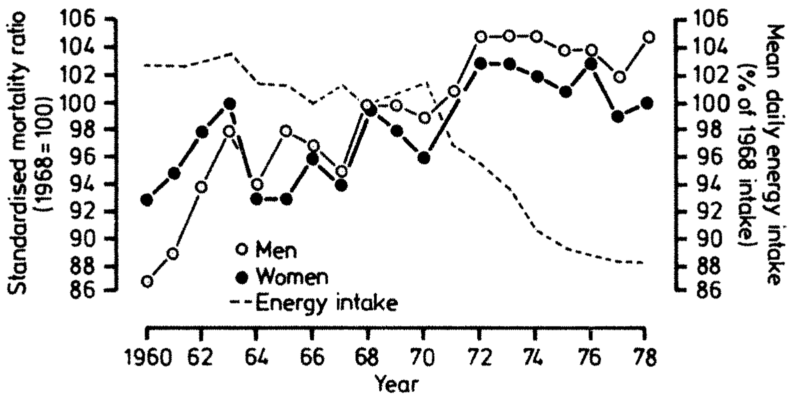

Fig. 1 *Trends of heart disease mortality (ICD 410–414 Eighth Revision) and energy intake 1960–78.*

Table 2 *Methodological details in prospective studies of diet and ischaemic heart disease*

Study	*Population (age range in yr)*	*No of subjects*	*Dietary survey method*	*Adverse outcome*	*Duration of follow up (yr)*
Framingham	Male (45–64)	831	24 hour recall	Death (ischaemic heart disease, acute myocardial infarction)	4
Zutphen	Male (40–59)	770	Cross check dietary history	Death (ischaemic heart disease)	10
Western Electric	Male (40–55)	1885	Dietary interview	Death (ischaemic heart disease, acute myocardial infarction, angina)	4·4
UK bankers and busmen	Male (30–67)	337	Seven day weighed survey	Death (ischaemic heart disease, acute myocardial infarction, angina)	10–20
Hawaii	Male, Japanese (45–68)	7590	24 hour recall	Death, (ischaemic heart disease, acute myocardial infarction)	6
Puerto Rico (Urban)	Male (45–64)	5714	24 hour recall	Death (ischaemic heart disease, acute myocardial infarction)	6
Puerto Rico (Rural)	Male (45–64)	2381	24 hour recall	Death (ischaemic heart disease, acute myocardial infarction)	6

Table 3 *Mean energy intake and disease status from seven longitudinal studies*

Study	*Patients with heart disease*				*Disease free subjects*			
	No	*Mean energy intake (cal$_{th}$)*	*SD*	*SEE*	*No*	*Mean energy intake (cal$_{th}$)*	*SD*	*SEE*
				High incidence areas				
Framingham	51	2369	700*	98·0	780	2622	700*	25·1
Zutphen	27	2857	582	112·0	743	3080	662	24·3
Western Electric	88	3082	974*	103·8	1797	3174	974*	23·0
UK bankers and busmen	50	2656	400	56·6	287	2869	505	29·8
				Low incidence areas				
Honolulu	179	2125	666	49·8	7411	2290	738	8·6
Puerto Rico (urban)	129	2242	856*	75·4	5585	2413	856*	11·5
Puerto Rico (rural)	34	2113	837*	143·5	2347	2353	837*	17·3

*Pooled standard deviation (SD) from patients and disease free subjects.
SEE, standard error of the estimate
Conversion: traditional to SI units—energy intake: 1 cal$_{th}$ ≈ 4·2 J.

Table 3 shows the mean energy intakes of those who did and did not develop ischaemic heart disease. It was necessary, in the absence of complete data, to use pooled standard deviations from both ischaemic heart disease patients and disease free subjects for the Framingham, Western Electric, and both the Puerto Rico population studies. This assumed that the variances were similar in the ischaemic heart disease patients as in disease free subjects. Though there was no a priori reason that they were different, a higher variance for the patients would have reduced the chances of any observed difference being statistically significant. The studies where separate data were available showed, however, that the variance tended to be lower for the patients (Table 3).

The most striking finding was that in each study the men developing ischaemic heart disease had, initially, a lower energy intake than the disease free men (Fig. 2), the difference varying between 100 and 250 kcal$_{th}$ (0·42 and 1·05 MJ) per day. These differences were significant for the Framingham, UK bankers and busmen, Hawaii, and the Puerto Rico (urban) studies. The data were pooled for both the combined high incidence areas and the combined low incidence areas. The design of the studies in the low incidence areas was identical, but this was not true for the high incidence areas (Table 2). Though the pooling would increase the chances of a statistically significant result by increasing the sample size, it nevertheless is of use in providing the best estimate of the true difference. Calculated 95% confidence intervals for the deficit in energy intake in ischaemic heart disease cases are for high incidence areas 141·4–278·6 kcal$_{th}$ (0·59 and 1·17 MJ) per day and for low incidence areas 96·6–253·4 kcal$_{th}$ (0·41 and 1·06 MJ) per day. The difference in means represents a shift to the left in the distribution of energy intake in the cases of ischaemic heart disease of 7·0% in the high incidence and 7·5% in the low incidence areas. It should be noted, however, that the difference in intake between high and low risk areas is greater than that between patients and disease free subjects within each of these two areas (Table 3).

Discussion

The evidence reviewed above is surprisingly consistent in suggesting an inverse association between energy intake and ischaemic heart disease risk within

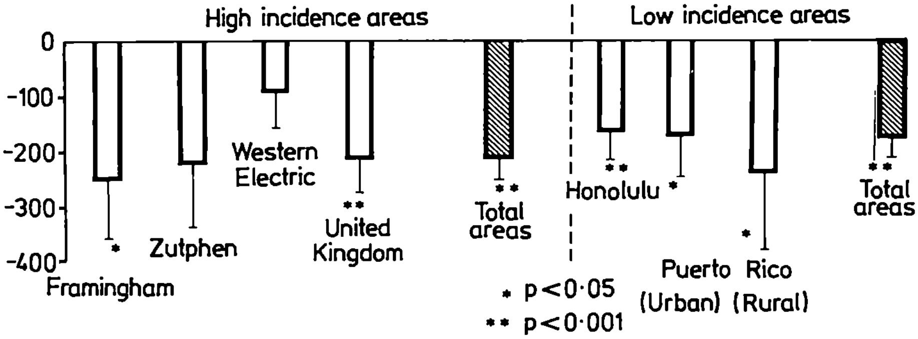

Fig. 2 *Difference and standard error of difference of total mean daily energy intake between patients with coronary artery disease and disease free subjects from seven logitudinal studies.*

population groups and conflicts with the evidence of the comparisons between countries[4 5] that countries with high levels of energy available for consumption have higher levels of ischaemic heart disease. The likely explanation for this paradox is that differences in energy intake between countries reflect relative affluence, and it is other variables associated with affluence that are the cause of the increased risk. The apparant protective effect of a high energy intake as suggested by the other studies described could possibly be explained by methodological problems and the possibility of confounding variables.

METHODOLOGICAL PROBLEMS

The association over time (Fig. 1) might be spurious. The National Food Survey data covered only food consumed at home, and during this period there had been an increase of 7% in meals taken away from home.[34] Thus apart from all the other hazards in interpreting such associations the data may not truly represent energy intake. Similarly, the retrospective studies cited[19–22] have to be interpreted with caution. Dietary inquiry in a retrospective or case-control study is open to error. Firstly, current diet may have altered as a result of disease presence and, secondly, a retrospective diet history is itself prone to error owing to poor recall.

The prospective studies cited used a single estimate of energy intake that might not reflect true intake over the duration of the study. Morris *et al* found a correlation of 0·73 within subjects for total energy intake calculated from two seven days weighed surveys performed one to 12 months apart.[35] Although the men in the Zutphen study showed pronounced changes between 1960 and 1965 and 1965 and 1976[36] there is no indication that the ranked order also changed. Thus, though diet does change, the originally observed differences are probably sustained. Furthermore, it is unlikely that any change over time is selectively different in direction between the ischaemic heart disease and disease free groups before the clinical onset of the disease. Secondly, the methods of dietary inquiry varied, and different end points and duration of study were used (Table 2). Estimates of energy intake from the methods used in all these studies probably underestimate true consumption.[37] The results were, however, similar and this consistency, despite the differences in method, is positive evidence in favour of the results being real.

Thirdly, it is possible that in the short term follow up those already with incipient ischaemic heart disease at the start of the study may, as a consequence, have had a lower energy intake. The short (two and a half to six years) duration of some of the studies[23 26 27 29 32 33] makes segregation between cause and effect difficult. The Zutphen men were, however, followed for 10 years,[28] and 10–20 years data are available from the UK bankers and busmen study[8] with, at the time of writing, a further six years of follow up analysed (Marr and Morris, unpublished data). These data for the UK men, despite the small numbers in each follow up period, show that there was no evidence that the trend was reversing (Kendall's tau 0·155, NS).

Fourthly, it is possible that obese persons may recall lower intakes. This possibility was examined in the Hawaii men,[32] and the authors concluded, "age adjusted mean values of total calories were consistently lower in IHD cases than in non cases in all classes of relative weight."

Finally, it is unlikely that these results are chance findings. The standard deviations are large, but the pooling of the studies together showed that the likelihood of a type I error was less than 1%.

POSSIBLE CONFOUNDING VARIABLES

It is possible that the relation to energy intake is explained by the confounding effect of other known ischaemic heart disease risk factors. The two most likely confounders are that both physical inactivity and cigarette smoking are associated with low energy intake, though the data are more substantive for the former. It was impossible, however, in the absence of direct access to all the raw data to do the necessary multiple logistic analyses to determine whether energy intake had an independent effect in the studies cited.

ENERGY EXPENDITURE

This is the likeliest confounding variable since in a steady state a high energy intake reflects increased muscular activity,[8] and the latter is possibly protective against ischaemic heart disease.[38,39] It has been found that a high energy expenditure is associated with an increased intake both in athletes[40,41] and office workers.[42,43]

In the prospective studies cited the patients with ischaemic heart disease in Hawaii[31] had lower levels of physical activity $(p<0{\cdot}05)$ compared with the disease free men, though the difference became statistically insignificant in multivariate analysis. The age adjusted mean energy intake was significantly lower in patients with ischaemic heart disease than in disease free subjects, even after controlling for physical activity.

The effect of increase in energy expenditure is, however, complex. Exercise does not, however, consistently increase the appetite.[44] An increase in daily exercise sufficient to produce weight loss over an eight week period did not increase energy intake,[45] and 45 minutes of light jogging three days a week also had no effect.[46] Indeed, in animals exercise may decrease the appetite.[47,48]

Cigarette smoking

There are no data on whether cigarette smoking is associated with a reduction in energy intake compared with non-smokers. Anecdotally, patients who give up smoking report an increase in energy intake with increase in body weight, but whether this is a phenomenon of all non-smokers (never and ex-smokers) is unknown. Analysis of the UK men, with smokers and non-smokers separately divided into equal high and low energy intake groups, showed that in both smoking groups the high intake group had approximately half the risk for ischaemic heart disease of the low intake group.[8]

BIOLOGICAL PLAUSIBILITY

In the absence of a plausible biological explanation a causal relation between low energy intake and ischaemic heart disease cannot easily be inferred from these data.[49] The only likely explanation is that high energy intake is associated with an increase in plasma high density lipoprotein cholesterol concentration, though this might be explained by the confounding effect of energy expenditure.

The results of an intervention study comparing the effect of an exercise programme with sedentary controls on energy intake, body weight, and blood lipid concentrations[50] showed an identical positive relation between mileage run with both increase in energy intake $(r=0{\cdot}48, p=0{\cdot}006)$ and increase in plasma high density lipoprotein cholesterol concentration $(r=0{\cdot}48, p=0{\cdot}006)$. The increase in energy intake included an increase in total fat consumption. It has, however, been shown that mild exercise in middle aged sedentary men has a favourable effect only on high density lipoprotein cholesterol concentration when energy intake is maintained; a reduction in intake leads to a reduction in high density lipoprotein concentration.[51] Thus perhaps increased exercise and increased energy intake act synergistically in reducing ischaemic heart disease risk rather than as confounding variables. An alternative hypothesis is to consider the effect that ischaemic heart disease risk is related to trace element deficiency in the diet,[52,53] and thus those with a high energy intake, assuming that they eat more of everything, might be less likely to show such deficiencies. Such hypotheses are virtually impossible to test without detailed and repeated chemical analyses of food and drink consumed, food tables being inadequate for the purpose. Such a methodology is likely to be unacceptable in free living populations participating in a prospective study.

BIOLOGICAL IMPORTANCE

It is of interest to note, however, that if the inverse association is causal its strength is high enough to be of biological importance. The observed difference in mean energy intakes represents a shift in the distribution, and a comparable shift, in proportionate terms, applied to other known risk factors would be likely to have a major effect on ischaemic heart disease rates.[54] As an example, the data from the UK bankers and busmen study[8] are given in Table 4, which shows that the magnitude of the difference observed in energy intake is comparable to the difference observed with

Table 4 *Relative difference in risk factors between men with ischaemic heart disease (group 1) and disease free men (group 2)*[8]

Variable	*Group 1*	*Group 2*	*Difference in group 1 as % of group 2*
Mean serum cholesterol concentration (mmol/l)	6·46	6·05	+ 6·8
Mean systolic blood pressure (mm Hg)	144	138	+ 4·3
Mean No of cigarettes per day	15·1	9·4	+60·6
Mean energy intake (kcal_{th})	2656	2869	− 7·4

Conversion: traditional to SI units—energy intake: 1 $\text{kcal}_{\text{th}} \approx 0{\cdot}0042$ MJ.

serum cholesterol concentration or systolic blood pressure.

Conclusion

There appears to be paradoxically an inverse association between energy intake and ischaemic heart disease risk within countries whose strength and consistency are similar to those of other established risk factors. The confounding effect of exercise or indeed other risk factors cannot be entirely discounted, though there is evidence that high energy intake and expenditure are synergistic.

There is no evidence that excessive energy intake in the absence of matched output is anything but harmful to health,[55] but there is support, we believe, for the hypothesis that there is a minimum energy intake—probably higher than that needed to maintain body weight in the sedentary middle aged man—below which the risk of ischaemic heart disease is increased.

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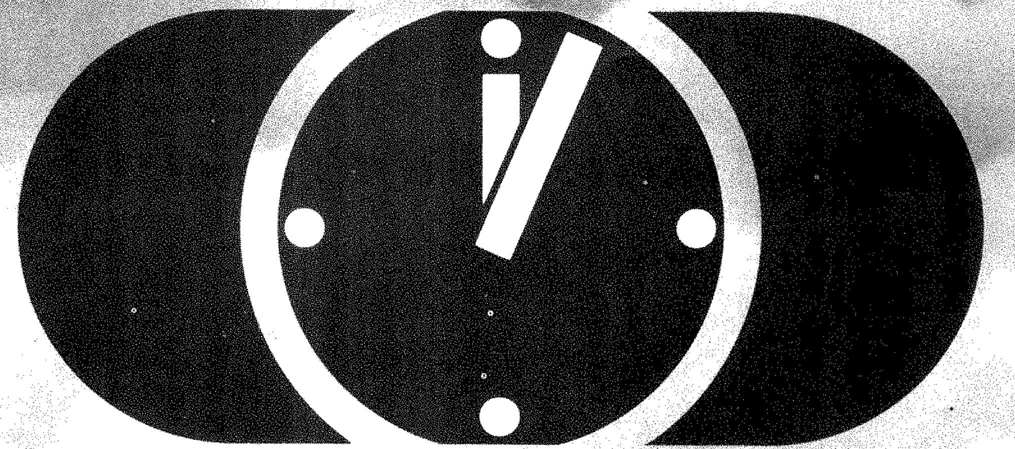
24 hour



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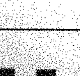
Angina, anxiety, essential tremor, thyrotoxicosis, prophylaxis of migraine.			
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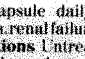
Hypertension where extra control is required.			

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Br Heart J 1985; 53: 631–5

Efficacy of transdermal glyceryl trinitrate in the treatment of chronic stable angina pectoris

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SUMMARY A study was carried out to assess the efficacy of a new transdermal preparation of glyceryl trinitrate (Transiderm-Nitro 5) in the 24 hour prophylaxis of angina and to determine the duration of effect of a single patch application. Twelve men with chronic stable angina were studied in a randomised, placebo controlled, double blind trial. By serial treadmill exercise testing a therapeutic effect was shown at three hours; the exercise time to angina and to 1 mm ST segment depression and the total exercise time were all significantly increased. At 24, 48, and 72 hours, however, no therapeutic effect was observed. Recent studies have shown a similar lack of effect at 24 hours for various forms of transdermal delivery systems. It is suggested that this lack of effect is due to the rapid onset of tolerance probably as a result of the constancy of blood concentrations obtained by this method of administration.

Inhaled amyl nitrite was the first drug to be used for the relief of angina pectoris, and its successor, sublingual glyceryl trinitrate, remains one of the standard forms of treatment.[1] The brevity of its action led to a search for longer acting preparations; thus various forms of oral nitrates became available and were shown to provide long term symptomatic benefit in ischaemic heart disease.[2-4] Nevertheless, rapid hepatic metabolism led to difficulties in dosage titration, and confusion exists as to which metabolite is responsible for its major effects.[5-7] Quite recently, nitrate creams applied to the skin have been shown to be efficacious since they avoid the problems of first pass hepatic metabolism.[8-10] These preparations are, however, messy to use, require frequent application, and do not permit accurate dosing.[11] Thus the recent development of a new transdermal delivery system to release glyceryl trinitrate into the circulation at a constant rate for 24 hours ought to represent a notable advance.[12-14] The transdermal system consists of a plaster patch containing a 25 mg reservoir of glyceryl trinitrate paste. A semipermeable, rate limiting membrane on the inner surface is applied to the skin. The glyceryl trinitrate reservoir maintains a concentration gradient and the rate limiting membrane maintains a constant delivery of 50 $\mu g/cm^2/h$. The absorption capacity of the skin is proportional to the depth and density of the capillary network; by applying the patch to the hairless skin of the trunk rather than to an extremity the rate of absorption is kept constant.[15-17]

This study was designed to test the efficacy and duration of action of a single glyceryl trinitrate patch.

Patients and methods

The trial was a randomised, double blind, crossover study. Twelve men (mean age 52·7 (range 33–66) years) completed the study. They were selected from a clinic population with chronic stable angina (median length of history 17 (range 4–56) months) and a positive exercise test (at least 1 mm horizontal or downsloping ST segment depression during treadmill exercise). Three of the 12 patients had concomitant medical conditions: one had hypercholesterolaemia, one hypertension, and one diabetes mellitus. Patients with unstable angina, recent myocardial infarction (within two months), valvar heart disease, heart failure, history of severe headaches, allergy to plaster, anaemia, Prinzmetal angina, and previous intolerance to nitrates were excluded. Antianginal agents other than beta adrenergic blockers and sublingual glyceryl trinitrate were withdrawn two weeks before the study. Nine patients were taking chronic beta blockade

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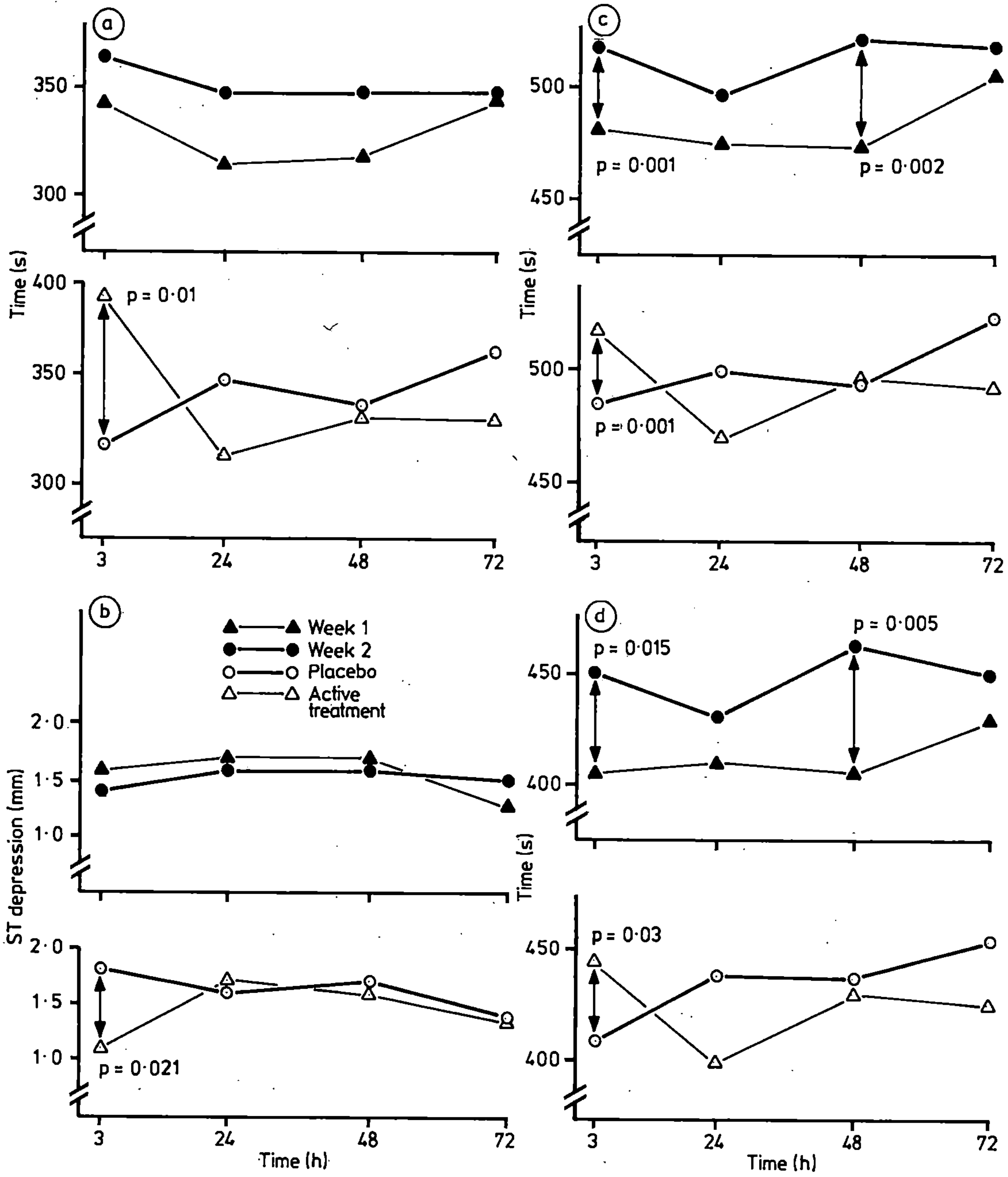

Figure *Mean results of (a) time to 1 mm ST depression, (b) ST depression at minimum exercise, (c) total exercise time and (d) time to angina during exercise testing at 3, 24, 48, and 72 hours of treatment in 12 patients receiving a glyceryl trinitrate patch or a placebo. The total values for week 1 and week 2 indicate the period effect or effect of training of serial exercise testing. The influence of training on the effects of treatment is allowed for in the calculation of the p values. Significant differences between two values are indicated by the bidirectional arrow.*

treatment, which was continued throughout the study.

The study consisted of a series of exercise tests performed over four successive days during two successive weeks with a three day break between each series of tests. Patients were randomised to receive either Transiderm-Nitro 5 or placebo treatment in their first week, receiving the other treatment in their second week. Exercise tests were performed at 3, 24, 48, and 72 hours after patch application using a modified Bruce protocol; the endpoint was a moderate, previously agreed level of angina. Twelve lead electrocardiograms were recorded at each minute of exercise and into recovery. For each patient the lead which showed the greatest ST segment depression during the first test was used for ST segment analysis on evey subsequent test.

The following variables were measured: (*a*) time to 1 mm ST segment depression (at 60 ms after the J point); (*b*) time to angina; (*c*) total exercise time; and (*d*) ST segment depression at minimum exercise. Since a number of factors other than angina influence the total exercise time we decided to measure also the ST segment depression at a standardised point in the exercise protocol as well as at the maximum exercise time. This was termed the minimum exercise time and was obtained by measuring the amount of ST segment depression observed during the shortest exercise test and comparing this with the ST segment depression observed at the same minute of exercise in the other seven tests.

Statistical analysis was performed using the two period crossover technique described by Grizzle,[18] a p value of $<0{\cdot}05$ being considered to be significant. Results are expressed as mean (SD).

Results

Seven patients received their active treatment during the first week and five received placebo. The results of serial exercise testing are shown in the Figure. During active treatment there were significant increases at three hours in the time to angina (446(100) *vs* 409(130) s, $p=0{\cdot}03$) and to 1 mm ST segment depression (384(100) *vs* 318(132) s, $p=0{\cdot}01$) and in the total exercise time (517(92) *vs* 484(118) s, $p=0{\cdot}01$). The amount of ST segment depression at the minimum exercise time was also less at three hours (1·1(0·5) *vs* 1·8(1·0) mm, $p=0{\cdot}02$). These results take into account the training effect produced by serial exercise testing—that is, the subjects performed as a group better during the second week of the trial regardless of their randomisation order (Figure). At 24, 48, and 72 hours, however, no beneficial effects were seen during active treatment. During exercise testing at three hours after application of the nitrate patch the heart rate, systolic blood pressure, and double product (heart rate multiplied by systolic blood pressure) at the onset of angina, at 1 mm of ST segment depression, and at peak exercise were not significantly different from placebo.

The period of treatment (72 hours) was too short to assess its effects on the frequency of angina during daily activities, and therefore angina diary cards were not used; none the less, two patients expressed a preference for the active patch, two for the placebo, and eight had no preference. Eleven patients reported headache and lightheadedness during active treatment, which in four persisted for 24 hours, in three for 48 hours, and in three for 72 hours. Six patients also complained of these symptoms while taking placebo. In one patient severe headache and vomiting occurred during the first 24 hours of active treatment. In no patient was there a skin reaction.

Discussion

Serial exercise testing in these 12 patients showed a small but significant benefit from transdermal glyceryl trinitrate at three hours after patch application but not at 24, 48, or 72 hours. Recent studies of transdermal nitrates have produced conflicting results. Reichek *et al* were unable to show any improvement in exercise tolerance at 4, 8, or 24 hours after transdermal glyceryl trinitrate delivered at almost twice the dosage used in the present study, although at very high dosage (equivalent to more than 20 mg of glyceryl trinitrate in 24 hours) a therapeutic effect was seen at four and eight but not at 24 hours.[19] Parker *et al*, testing a patch containing 100 mg of isosorbide dinitrate, found that exercise performance was improved at two, four, and eight hours but not at 24 hours.[20] Naaes *et al*, evaluating a glyceryl trinitrate patch, found a significant improvement in exercise tolerance at 12–16 hours but did not test efficacy at 24 hours.[21] Cerri *et al* tested two glyceryl trinitrate patches (Nitroderm TTS 5 and Nitroderm TTS 10) and found significant improvement in exercise tolerance at three and 24 hours, although there was no difference between the patches.[22] On the basis of these studies, some scepticism that transdermal nitrate patches provide 24 hour prophylaxis in angina is justified.[23 24]

In our study, the absence of any therapeutic benefit at 24 hours and thereafter may have been due either to subtherapeutic plasma concentrations of glyceryl trinitrate or to the loss of end organ responsiveness—namely, tolerance. While the plasma concentrations obtained from a single Transiderm-Nitro 5 patch are relatively low compared with those reported with other long acting nitrate preparations,[16] the plasma concentrations have been shown to be constant for up to 28 hours.[12–14] The plasma concentration is closely related to the surface area available for absorption[15–17] and can be raised by increasing the size of the patch or applying more patches simultaneously. Thus in one study the glyceryl trinitrate concentration obtained from four patches applied simultaneously was more than three times greater than from a single patch.[17] Our data show, however, that a single application is sufficient to produce a significant, albeit small, therapeutic effect accompanied in almost all patients by headache. If it is assumed that diffusion has remained constant for 24 hours then the loss of therapeutic effect suggests the rapid development of tolerance. Muller *et al* in their studies using transdermal glyceryl trinitrate noted an attenuation of the haemodynamic responses to the patch measured in the afternoon compared with the morning, although plasma concentrations of glyceryl trinitrate had not fallen.[17] Tolerance has been found within 24 to 48 hours of commencing regular six hourly treatment with isosorbide dinitrate at both low and high dosage.[25 26] In the recent study cited above, Parker *et al* were unable to show any benefit whatsoever from transdermal isosorbide dinitrate after 7–10 days of treatment, despite the initially significant therapeutic effect.[20] There is evidence that any nitrate preparation which produces constant plasma concentrations and which therefore does not allow time for reversal of tolerance may quickly become ineffective.[25] Parker *et al* have shown that the initial tolerance which occurs during chronic treatment may still be overcome by sublingual glyceryl trinitrate,[20] again suggesting that haemodynamic responsiveness is dependent on rapid fluctuations in plasma concentrations. The mechanism of tolerance is unknown, but an opposing reflex neurohumoral vasoconstrictor response has been suggested.[27]

In other placebo controlled studies with long acting nitrates a higher rate-pressure product was achieved during active treatment. That this was not observed in our 12 patients may have been due to the attenuating effects of beta blockade in nine of them. Nevertheless, others have also found a lack of effect on the double product with nitrate patches used alone.[19 20] Nitrates are effective in patients taking beta blockers,[28] and the continued use of them throughout the study period should not have reduced the therapeutic effect of transdermal glyceryl trinitrate.

The stepwise improvement in exercise performance induced by training during a serial exercise training programme is well shown in this study by the observation that mean exercise time to angina and the duration of exercise were significantly greater during the second period compared with the first (Figure). Any consequent bias, which was in fact slightly in favour of placebo, was excluded by using the Grizzle two period changeover analysis in the calculation of the p values.[18]

In conclusion, a single patch containing 25 mg of glyceryl trinitrate produced a therapeutic effect on exercise performance at three hours after application, but this was not maintained at 24 hours or thereafter. It is likely that his loss of effect was due to the rapid development of tolerance, which may be related to the constant blood concentrations achieved by this delivery system. There is evidence that fluctuation of blood concentrations may be necessary to maintain haemodynamic responsiveness.[20 25] A more significant benefit might be derived from a larger patch, but side effects could limit the efficacy of such a preparation, and even in a high dose the therapeutic effect seems to be lost by 24 hours. In view of the relatively high cost of this transdermal system compared with conventional, orally administered long acting nitrates, we suggest that further studies are necessary before this method of nitrate treatment be recommended for patients with chronic stable angina.

We thank Geigy Pharmaceuticals for supplying the active and placebo patches and for assistance with analysis of the data, Drs J Russell Rees, S C Jordan, and J Vann Jones for allowing us to study patients under their care, and Mr L M Clarke and his staff for technical assistance.

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Clinical value of Doppler echocardiography in the assessment of adults with aortic stenosis

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SUMMARY Continuous wave Doppler echocardiography was used to study 41 adults with clinically suspected aortic stenosis undergoing cardiac catheterisation. Non-invasive assessment of the severity of stenosis was made before catheterisation using electrocardiograms, chest radiographs, and cross sectional echocardiography in addition to clinical examination and assessment modified, where appropriate, by the result of the Doppler examination. Catheterisation gradients were obtained in 33 patients and correlated well with those obtained by Doppler examination particularly when simultaneous recordings were obtained. All patients with surgically significant stenoses were identified by non-invasive assessment including Doppler examination and overestimation was not found in any patient with a less than significant stenosis.

Thus surgery can be recommended in patients with aortic stenosis without the need for previous cardiac catheterisation.

Cross sectional echocardiography is a well established non-invasive method of assessing the severity of valvar stenoses. It is of particular value in the assessment of mitral stenosis,[1] but difficulties can arise in accurately assessing patients with aortic stenosis.[2 3]

The ability of Doppler echocardiography to measure transvalvar gradients has obvious potential benefits in the non-invasive assessment of patients with aortic stenosis. Pulsed wave Doppler ultrasound has been used to measure blood flow velocity in the ascending aorta[4] and to establish normal values.[5] Nevertheless, it is unable to measure the high velocities present in patients with aortic stenosis, a disadvantage not found with the continuous wave Doppler technique. Using the continuous wave Doppler technique recent reports have suggested that in patients with aortic stenosis there is a good correlation between the Doppler derived gradient and that obtained at catheterisation,[6–8] but the potential clinical application of the technique has yet to be fully established. This study was therefore undertaken in patients with clinically suspected aortic stenosis to confirm the accuracy of continuous wave Doppler ultrasound in predicting valve gradients and in particular to assess its clinical value and possible role in the subsequent management of these patients.

Patients and methods

The study group comprised 41 adults (age range 14–73 (mean 52) years) undergoing cardiac catheterisation with clinically suspected aortic stenosis either alone or in combination with other valve lesions. All patients had clinical examination performed by two experienced cardiologists. In addition a 12 lead electrocardiogram, chest radiograph, and cross sectional echocardiogram were performed in all patients before cardiac catheterisation.

DOPPLER ECHOCARDIOGRAPHY

Doppler examination was performed using a Vingmed Alfred continuous and pulsed wave velocimeter with a 2 MHz transducer. Continuous wave velocimetry was used for all examinations to obviate the effects of aliasing occurring in the measurement of high velocities in the pulsed mode. Being both gain and threshold dependent there is a tendency for the analogue display of maximum velocity to underestimate valve gradient,[6] and so spectrum analysis was used in all cases, using either an Angioscan or Doptek analyser. Doppler examination was performed in the resting state from a variety of precordial positions in order to

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obtain the Doppler signal of maximum systolic blood flow velocity in the ascending aorta. The audio signal was used in addition to spectrum analysis to obtain the Doppler signal indicating laminar flow and the maximum systolic frequency shift then obtained from a clearly demarcated spectral signal without obvious interference (Fig. 1). In an attempt to minimise the risk of falsely low recordings all possible precordial positions were examined including suprasternal, apical, subcostal, supraclavicular, and right parasternal in the right lateral decubitus position.

The maximum systolic velocity obtained in the ascending aorta by the Doppler examination was used to calculate the transvalvar gradient using a modification of the Bernoulli formula[9]; $P=4V^2$ where P is the transvalvar gradient (mm Hg) and V the maximum systolic velocity (metres s^{-1}). Before cardiac catheterisation an assessment of the severity of aortic obstruction was made by the attending physician using clinical examination with the addition of an electrocardiogram, chest radiograph, and cross sectional echocardiogram. This was graded as either non-significant, surgically significant, or severity in doubt from non-invasive information. The result of the Doppler examination was then added and any appropriate modification of the assessment of severity made.

CARDIAC CATHETERISATION

All patients underwent full cardiac catheterisation using Judkins's technique and where possible peak to peak systolic gradients (in mm Hg) obtained by withdrawal of a fluid filled multihole catheter across the aortic valve. In addition two patients underwent transseptal catheterisation using the Brockenbrough technique in one and via a patent foramen ovale in another. All patients were prescribed 10 mg diazepam orally as a premedication 30 minutes before catheterisation. This may have the effect of lowering cardiac output and transvalvar gradient. In an attempt to assess the effects of sedation on the aortic valve gradient 24 of the 33 patients had a further Doppler examination performed at the time of cardiac catheterisation immediately after withdrawal of the catheter across the aortic valve.

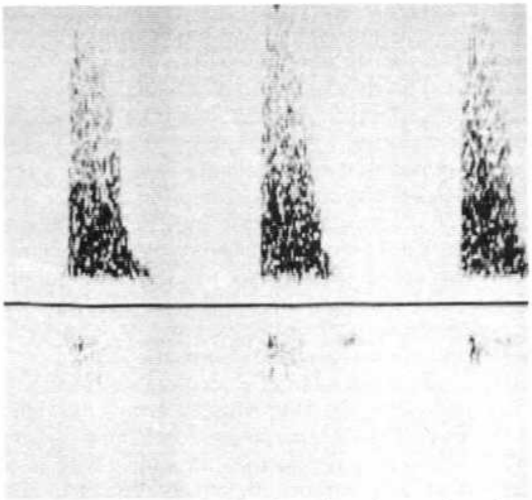

Fig. 1 *Continuous wave Doppler echocardiogram from the suprasternal notch indicating a clearly demarcated spectral signal in a patient with an aortic valve gradient of 37 mm Hg.*

The decision regarding subsequent patient management was made by the attending physician on the basis of all available clinical and non-invasive data in addition to the results of cardiac catheterisation, and a comparison could then be made with the decision reached by non-invasive techniques alone.

Results

Satisfactory Doppler signals were obtained in all patients. Though the suprasternal notch was the most successful position for obtaining the optimum Doppler signal (29 of 41 patients) it was not possible to predict the most satisfactory precordial examination position even when cross sectional echocardiography was used. Indeed, although several positions were usually successful in each patient, the right parasternal position was most successful in six, the subcostal in five, and the apical in one, and in one patient the only satisfactory view was obtained from the right supraclavicular position.

In eight of the 41 patients undergoing cardiac catheterisation it was not possible to cross the aortic valve retrogradely. Transseptal catheterisation was not undertaken at the discretion of the attending physician and therefore no gradients were obtained in these patients.

In the remaining 33 patients the catheter gradients ranged from 0 to 120 mm Hg with a mean of 43 mm Hg and the Doppler gradients from 8 to 157 mm Hg with a mean of 49 mm Hg. Figure 2a shows the overall correlation between the catheter derived gradients and those obtained by Doppler. In addition, the correlation between the Doppler derived gradients obtained simultaneously at catheterisation and the catheter gradients is shown (Fig. 2b). A superior correlation ($r=0\cdot98$) was obtained by this method, presumably because of the effects of sedation. This is suggested by the fact that in the majority (70%) Doppler gradients obtained simultaneously at catheterisation were lower than those obtained without the effects of sedation.

In the 33 patients in whom valve gradients were subsequently obtained at catheterisation the non-invasive assessments with and without Doppler measurements were compared with the subsequent outcome from the complete data including that obtained at catheterisation. Though in general terms a peak aortic gradient of >50 mm Hg was taken as surgically significant in one patient the gradient at Doppler examination was 42 mm Hg and 45 mm Hg at catheterisation. This was regarded as significant by the attending physician and therefore analysed as such.

In the nine patients with clinically non-significant lesions the Doppler findings suggested a non-significant lesion in seven, which was subsequently confirmed by catheterisation. In the remaining two patients, however, Doppler examination suggested a surgically significant lesion, which was confirmed by catheterisation in both cases.

In the 12 patients thought clinically to have surgically significant aortic stenosis Doppler examination identified a surgically significant gradient in all 12, which was subsequently confirmed by catheterisation. The remaining 12 patients, however, had inconclusive evidence on clinical and non-invasive data. In 10 patients Doppler examination could not identify a significant gradient nor did subsequent catheterisation. The two surgically significant lesions detected by the Doppler technique were, however, confirmed by catheterisation.

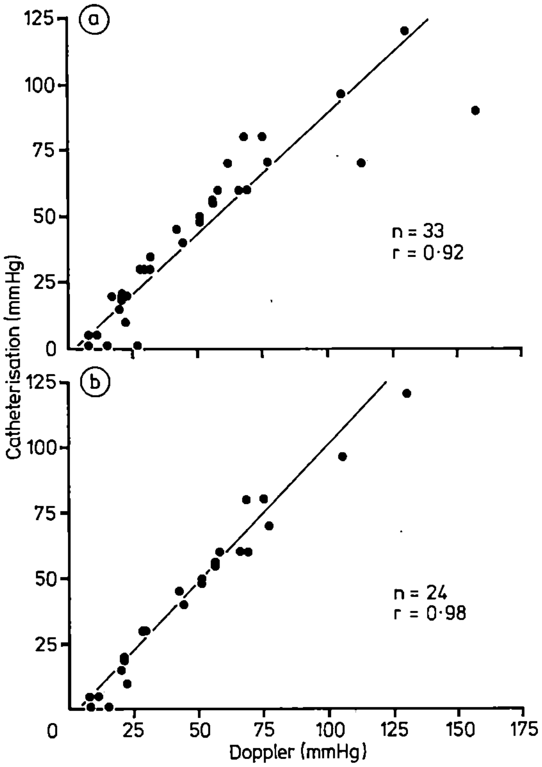

Fig. 2 *Correlation of valve gradients obtained using the continuous wave Doppler technique and (a) those subsequently found at cardiac catheterisation and (b) those obtained at simultaneous cardiac catheterisation.*

Discussion

It has been suggested that the non-invasive assessment of valve disease can obviate the need for cardiac catheterisation in many cases.[10] Patients with aortic stenosis are, however, often the most difficult to assess non-invasively, and cardiac catheterisation is almost always required. In this study, however, in an appreciable number of patients (eight of 41) it was not possible even at cardiac catheterisation to obtain a valve gradient. In comparison satisfactory signals were recorded in all patients investigated by the Doppler technique.

The correlation found between the Doppler derived gradient and that obtained at catheterisation indicates that Doppler echocardiography provides an accurate assessment of the gradient across an aortic obstruction. This measurement did not appear to be appreciably affected by the fact that peak to peak systolic gradients were measured at catheterisation rather than an instantaneous value as measured by the Doppler technique.[11] In several cases the sedative used as a premedication for catheterisation affected the Doppler derived gradient, slightly lowering its value compared with previous Doppler examinations. This probably accounts for the better correlation between simultaneous recordings and also for the less accurate correlations reported in other studies where simultaneous measurements were not made.[8 9]

The potential for falsely low recordings by the Doppler technique is, however, an important consideration. In our study no falsely low recordings were obtained. This may be due in part to the care taken in performing Doppler examinations from all available precordial positions in all patients. Nevertheless, it can be argued that by attempting to measure a very small high velocity jet at an unknown angle, the possibility of false negative recordings by the Doppler technique must exist. Therefore extreme care should be taken in interpreting the result of a Doppler examination that suggests a less than significant obstruction where this is at variance with either the clinical or routine non-invasive examinations.

More important than the accurate correlation of valve gradients with catheterisation data is the ability of the Doppler technique to help determine the subsequent clinical management of the patient with aortic stenosis when integrated as part of a complete non-invasive assessment. Indeed in our study no patient with a surgically significant lesion would have been missed by complete non-invasive assessment including Doppler examination, and in no patient was there an appreciable overestimation of the severity of obstruction. Where doubt existed as to the severity of a lesion by other non-invasive techniques alone, Doppler examination was able to correctly clarify the degree of obstruction in all cases. Possibly more important is the fact that the Doppler examination identified two patients with surgically significant lesions that would otherwise have been missed by routine clinical and non-invasive assessment.

It can be argued that cardiac catheterisation may be indicated for other valve lesions, but, as previously reported, the vast majority of these can be accurately assessed by standard non-invasive techniques.[10] Where the possibility of ischaemic heart disease exists coronary angiography may be indicated, but this is a much less hazardous and time consuming procedure than full right and left heart catheterisation. Indeed in an appreciable number of patients undergoing catheterisation for valvar disease coronary angiography is not performed.[10]

Doppler echocardiography has therefore added a new dimension to the assessment of patients with aortic stenosis. When combined with clinical examination and other routine non-invasive techniques it can accurately determine the subsequent clinical management of these patients, and it would therefore seem safe and appropriate to recommend surgery in an appreciable number of patients with aortic stenosis without the need for previous cardiac catheterisation.

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Increased blood velocities in the heart and great vessels of patients with congenital heart disease

An assessment of their significance in the absence of valvar stenosis

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SUMMARY During a previous investigation and during routine clinical Doppler echocardiography velocities distal to normal valves were found to be increased in patients with congenital heart disease. To investigate this observation the velocity proximal and distal to cardiac valves was recorded in 56 patients with congenital heart disease. No detectable pressure gradient had been found across these valves at catheterisation and no velocity gradient >20 cm/s was found across them by range gated Doppler echocardiography. In 82% of the patients, however, the blood velocity across one or more valves exceeded normal limits. Increased velocities were found at the tricuspid inflow (55%), pulmonary artery (38%), mitral inflow (34%), and ascending aorta (11%). Factors predisposing to the presence of increased velocities in these areas were increased flow through the valve and decreased compliance of the receiving chamber.

This study shows the necessity for recording velocity both proximal and distal to a valve before a gradient is calculated according to the modified Bernouilli equation.

Doppler interrogation of velocities in the heart and great vessels is now an accepted diagnostic procedure. Previous physical,[1] angiographic,[2] and Doppler investigations[3] have shown that flow through stenotic valves produces a jet and that the velocity of the jet is related to the magnitude of the pressure gradient, which may be calculated using a modification of the Bernouilli equation.[4 5] This modified formula is as follows: pressure gradient = $4(V2^2-V1^2)$ where V2 is the velocity (m/s) distal to the valve and V1 is the velocity (m/s) proximal to the valve.

In practice, however, it is usual to ignore the proximal velocity because its inclusion would not have a major influence on the result. Accordingly, most increased velocities are assumed to be due to stenosis, and a gradient is calculated on the basis of the increased distal velocity alone.

During the course of many clinical Doppler examinations of children with congenital heart defects, we found that some patients without stenotic lesions had velocities in the central circulation that exceeded values found in normal populations. The purpose of this investigation was to identify situations in which these increased values might be expected.

Patients and methods

The study population consisted of those patients with congenital heart disease studied by Doppler echocardiography in Killingbeck Hospital between February and May 1984 who met the following criteria: (*a*) confirmation of diagnosis by cardiac catheterisation (except in the case of those patients with an isolated ductus arteriosus who were normal on physical examination after ligation, (*b*) measurement of pressure proximal and distal to all valves at cardiac catheterisation, and (*c*) no significant difference in blood velocity or pressure measurement across the valve of interest. Several patients with stenotic valves were included (Table), but the velocity across the

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Table *Peak velocity measurements of bloodflow distal to each valve*

Case No	*Age (yr)*	*Diagnosis*	*Postvalve velocity (cm/s)*			
			Tricuspid	*Mitral*	*Pulmonary*	*Aortic*
1	9	Aortic stenosis	50	105	65	Jet
2	7	Aortic stenosis	35	105	90	Jet
3	2	Aortic stenosis	70	122	82	Jet
4	4	Aortic stenosis	30	136	70	Jet
5	8	Aortic stenosis	72	68	68	Jet
6	7	Aortic stenosis	62	114	98	Jet
7	8	Aortic stenosis	40	130	48	Jet
8	29	Aortic stenosis	42	142	96	Jet
9	0·4	Aortic stenosis, coarctation of aorta	45	120	78	Jet
10	2	Aortic stenosis, coarctation of aorta	42	140	65	Jet
11	4	Atrial septal defect	86	66	78	150
12	14	Atrial septal defect	84	75	236	102
13	7	Atrial septal defect	105	80	155	125
14	8	Atrial septal defect	92	82	120	108
15	8	Atrial septal defect	79	85	102	100
16	15	Atrial septal defect	90	90	170	130
17	1	Atrial septal defect	150	92	Jet	106
18	2	Atrial septal defect	78	122	148	102
19	7	Atrial septal defect	118	108	160	109
20	0·9	Atrial septal defect, pulmonary hypertension	136	105	110	105
21	1	Complete transposition, postoperative	80	62	Jet	50
22	0·6	Complete transposition	65	60	90	90
23	15	Complete transposition, ventricular septal defect, pulmonary stenosis, postoperative	109	108	Jet	104
24	3	Atrioventricular septal defect	88	98	158	106
25	0·6	Atrioventricular septal defect, persistent ductus arteriosus	140	140	194	140
26	3	Parachute mitral valve	62	Jet	76	140
27	10	Persistent ductus arteriosus	65	82	105	135
28	1	Persistent ductus arteriosus	42	102	92	204
29	6	Persistent ductus arteriosus	46	131	70	161
30	0·1	Persistent ductus arteriosus	68	136	Jet	205
31	2	Persistent ductus arteriosus	65	150	120	205
32	5	Pulmonary stenosis	34	60	Jet	108
33	5	Pulmonary stenosis	54	76	Jet	116
34	0·5	Pulmonary stenosis	55	82	Jet	80
35	1	Pulmonary stenosis, atrial septal defect	140	65	Jet	84
36	7	Systemic hypertension	105	142	106	145
37	2	Tricuspid atresia	—	130	40	98
38	2	Total anomalous pulmonary venous connection	89	90	210	120
39	0·8	Complete transposition, postoperative	112	60	Jet	70
40	0·3	Complete transposition, postoperative	95	80	100	100
41	0·1	Complete transposition, postoperative	100	80	140	106
42	4	Tetralogy of Fallot	85	50	Jet	80
43	4	Tetralogy of Fallot	80	60	Jet	80
44	1	Tetralogy of Fallot	78	62	Jet	80
45	4	Tetralogy of Fallot	94	78	Jet	90
46	3	Tetralogy of Fallot	65	80	Jet	70
47	4	Tetralogy of Fallot	102	100	Jet	112
48	29	Tetralogy of Fallot, pulmonary incompetence, postoperative	88	94	92	68
49	25	Tetralogy of Fallot, pulmonary incompetence, postoperative	95	52	132	72
50	4	Tetralogy of Fallot, pulmonary incompetence, postoperative	113	88	120	102
51	10	Ventricular septal defect	64	116	160	118
52	0·4	Ventricular septal defect	60	120	78	120
53	1	Ventricular septal defect, pulmonary hypertension	92	120	120	116
54	5	Ventricular septal defect, pulmonary stenosis	70	52	Jet	60
55	0·3	Ventricular septal defect, pulmonary hypertension	80	120	103	120
56	0·1	Ventricular septal defect, pulmonary stenosis	102	118	Jet	70

Jet, high velocity flow associated with valvar stenosis.

stenotic valve was not of interest to this study. For example, a child with known pulmonary valvar stenosis was included if all three criteria were satisfied, but the pulmonary velocity was not included in this study. Nevertheless, velocities proximal and distal to the other three valves were appropriate to the interests of this study.

ECHOCARDIOGRAPHY

A complete cross sectional echocardiographic and range gated Doppler examination was performed on each patient.[6] Mitral and tricuspid velocities were measured in the apical four chamber plane according to previously described techniques.[7] The sample volume was initially placed distal to the valve and was

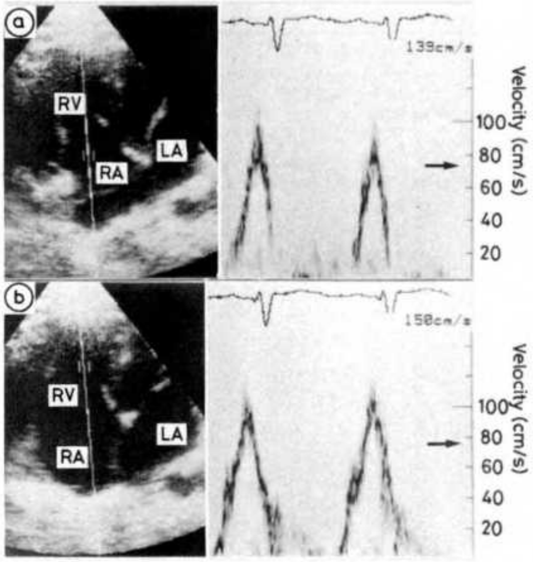

Figure *Cross sectional echocardiogram and time-velocity trace in a patient with pulmonary stenosis. The alignment of the ultrasound beam is shown by a highlighted line passing from the right ventricle (RV) to the right atrium (RA). The arrow indicates the upper limit of tricuspid velocity in normal individuals (77 cm/s). The sample volume for Doppler recording is shown as two short lines astride the Doppler cursor line (a) just proximal to the tricuspid valve leaflets and (b) just distal to the tricuspid valve leaflets. The velocity trace shows blood flow at a velocity slightly higher but still within 20 cm/s of the velocity proximal to the valve.*

aligned with the expected direction of flow as determined from the cross sectional echocardiographic image. The transducer was then moved in the plane of that image to achieve the highest velocity and the least spectral broadening, which occur concurrently when alignment with flow is achieved. After that location was identified the transducer was moved in the unseen (elevational) plane to maximise velocity and to minimise spectral broadening. This process allowed spatial alignment with flow. Accordingly, no correction was necessary for the intercept angle between the ultrasound beam and the direction of blood flow. Velocity distal to the valve was then recorded. Finally, the sample volume was placed proximal to the valve and the spatial alignment procedure repeated. The proximal and distal velocities were compared taking a mean of three to five cardiac cycles in each case. If the modal peak velocity for the two measurements was within 20 cm/s no true velocity difference was considered to be present across the valve. The process for measurement of velocities across the semilunar valves was similar, but different planes of ultrasound examination were used. Velocities across the pulmonary valve were studied from a high precordial short axis plane and velocities across the aortic valve were measured with an off axis imaging transducer from a short axis position in the suprasternal notch.[7] This transducer permits Doppler interrogation of the ascending aorta and left ventricular outflow tract parallel to blood flow. The spatial alignment with flow direction was accomplished in these planes according to the same method described for the atrioventricular valves.

Results

STUDY POPULATION

During the study period 482 patients with congenital heart disease underwent Doppler studies at Killingbeck Hospital. Four hundred and twenty four patients were excluded because (*a*) they had not undergone cardiac catheterisation (the most common reason) or (*b*) they had undergone catheterisation but did not have a measurement of pressure across the valve(s) of interest or, in a few instances, because a complete Doppler study was not or could not be performed. Fifty eight patients met the criteria for inclusion into the study. We were, however, unable to align satisfactorily with flow proximal to the aortic valve in two patients, who were then excluded. Accordingly, 56 patients formed the study group.

DOPPLER ECHOCARDIOGRAPHY

Measurement of velocity proximal and distal to the atrioventricular valves presented no problem. Alignment with the left ventricular outflow tract required the beam to be directed more anteriorly than is usual to image the ascending aorta. Although satisfactory results could be obtained for all but two patients, some experienced mild discomfort. The major problem was that the pressure of the transducer on the larynx caused some patients to cough almost continuously when the transducer was in position to image the outflow tract; severe paroxysms of coughing resulted in the exclusion of the two patients mentioned above. Interrogation of the pulmonary outflow tract and main pulmonary artery presented, in a few patients, a problem of beam-flow intercept angle. Although it was possible to achieve alignment with flow in the main pulmonary artery, an intercept angle as large as 30° was occasionally found at the level of the pulmonary valve. Although it was easy to determine the presence or absence of a velocity difference by sampling immediately proximal and distal to the valve, the absolute velocity measured at this site was less than in the centre of the distal main pulmonary artery because the intercept angle was less favourable at the valve than at the centre of the main pulmonary artery.

PREVALENCE OF VELOCITIES EXCEEDING NORMAL

To determine which velocities exceeded normal, we used the data previously collected in this unit by the same techniques.[8] Values exceeding the mean by 2 standard deviations or more were considered abnormal. The upper limits of normal velocity distal to the four cardiac valves were: tricuspid 77 cm/s, pulmonary 115 cm/s, mitral 109 cm/s, and aortic 142 cm/s. The Figure shows an example of a velocity in excess of normal. When jet velocities were excluded only 10 of 56 (18%) patients had all other velocities within the normal range (Table).

Increased tricuspid velocities

Thirty one of 55 (56%) had tricuspid velocities in excess of the normal range. Most patients with normal tricuspid velocities had lesions affecting mainly the left heart: aortic stenosis (10), parachute mitral valve (one), persistent ductus (five). Many patients with a variety of other lesions also had normal velocities. The common features of those with increased velocities (with the single exception of case No 36, Table) were either the presence of (*a*) lesions associated with increased right heart flow—atrial septal defect (10), atrioventricular defects (two), and pulmonary regurgitation (three); or (*b*) lesions causing increased resistance to flow into the right ventricle—tetralogy of Fallot (five), pulmonary stenosis (one), complete transposition (five), and ventricular septal defect associated with pulmonary hypertension (three) or with pulmonary stenosis (one).

Increased pulmonary velocities

All 17 patients with pulmonary jets were excluded from consideration. Fifteen of the remaining 39 (38%) had increased pulmonary velocities. All of these patients had either increased pulmonary blood flow due to left to right shunts (13/15) or pulmonary valve regurgitation (2/15). Nevertheless, 10 of the 24 who had normal pulmonary artery velocities also had increased pulmonary flow. Twelve of the remaining 14 with normal pulmonary velocities had left sided obstructive lesions—aortic stenosis (10), parachute mitral valve (one), or systemic hypertension (one).

Increased mitral velocities

All but one (case 18, Table) of the 19 patients with increased mitral velocity had lesions that caused increased mitral flow—ventricular septal defect (five), ductus arteriosus (four), tricuspid atresia (one)—or defects which caused aortic outflow obstruction—aortic stenosis with or without coarctation (seven), and systemic hypertension (one). Normal mitral velocities were found in a variety of conditions—tetralogy (nine), atrial septal defect of the secundum or endocardial cushion type (11), complete transposition (six), pulmonary stenosis (four), ventricular septal defect (two), ductus arteriosus (two), and aortic stenosis (three).

Increased aortic velocities

Six patients (11%) had increased aortic velocities, and only four of these were increased by more than 10%. All patients with a more than 10% increase had increased aortic flow due to a ductus arteriosus. Two others had minor increases, one with systemic hypertension and one with an atrial septal defect. All remaining patients, including one with increased aortic flow due to a ductus arteriosus, had velocities within the normal range.

Discussion

The important finding of this investigation is that many children with congenital cardiac malformations have blood velocities that exceed normal limits at sites within the heart that do not contain stenotic lesions. Accordingly, erroneous conclusions might be reached if velocities distal to the valve were used exclusively to calculate pressure gradients according to the modified Bernouilli equation. If the velocities proximal to the valves were neglected, the range of postvalve velocities found in many of our patients would have led to the erroneous identification of stenotic lesions albeit of a relatively minor degree. Strong evidence that the increased distal velocities in this population were not due to stenotic lesions is shown by the presence of equal or nearly equal velocities proximal and distal to the valve of interest. The results of this study clearly show that high velocity alone is not an indicator of valvar stenosis. We allowed a mean peak velocity difference of 20 cm/s between the two sites before a stenosis was considered to be present because this value was the highest velocity difference across a valve observed while studying a normal group.

The patient group was neither representative of the general population nor of the total population of children with cardiac malformations because, with the exception of those with a ductus arteriosus, all were selected for cardiac catheterisation. Accordingly, it is probable that a different percentage of individuals with increased velocities would be found in a different population. The important finding, however, is the existence of increased velocities rather than a measure of their precise occurrence rate.

Two factors, increased flow and increased resistance to flow, were associated with increased peak velocity. Other, as yet unidentified, factors may also exist. Increased flow has been mentioned by Hatle and Angelsen as a cause of increased velocity,[9] and we have reported data from a small series of patients with ductus arteriosus that substantiates this.[10] The finding is not surprising because velocity must increase when a higher than normal volume is delivered through a conduit or orifice of fixed dimension assuming that all other factors remain unchanged. The present investigation was not designed to determine the relation between peak velocity and flow because two other factors, the area through which flow passes and systolic time per beat, are also important in determining the peak velocity for any given flow rate.

Mitral and aortic velocity almost always exceed tricuspid and pulmonary velocity in the normal subject.[8 9] This finding has been attributed to the relatively decreased distensibility of the left ventricle and systemic circulation compared with that of the right ventricle and pulmonary circulation. We are not, however, aware of any previous reports regarding the requirement of increased velocities to fill ventricles or vascular beds characterised by decreased compliance. Our findings in this respect remain descriptive because the present investigation was not designed to determine the precise magnitude of peak velocity required to distend a chamber or vascular bed of reduced compliance at a given flow. Such a study would not be possible on the basis of gradient or wall thickness alone.

Pressures across valves were measured at catheterisation using fluid filled catheters and pullback tracings rather than with two catheters with pressure manometers mounted at their tips. Accordingly, some small gradients could have been missed. Our Doppler methodology allowed a difference in velocity between the areas proximal and distal to the valve of 20 cm/s. This velocity difference could account for a pressure gradient of 1–4 mm Hg depending on whether it occurred at the lowest or highest measured velocity. It seems unlikely that large gradients were missed by either method. Clearly, however, some patients with postvalvar velocities similar to those in the study had catheterisation and Doppler determined pressure gradients, sometimes called flow gradients, but these patients were excluded from this study by design because we were concerned only with those patients who had an increased postvalve velocity in the absence of a measured pressure gradient.

Some patients with increased flows or suspected decreased compliance had normal velocities. In these patients alterations in other factors—for example, conduit or orifice dimension or a long systolic time—may have permitted lower velocities. Nevertheless the results suggest that increased velocities are often required to accommodate high flow rates and decreased compliance.

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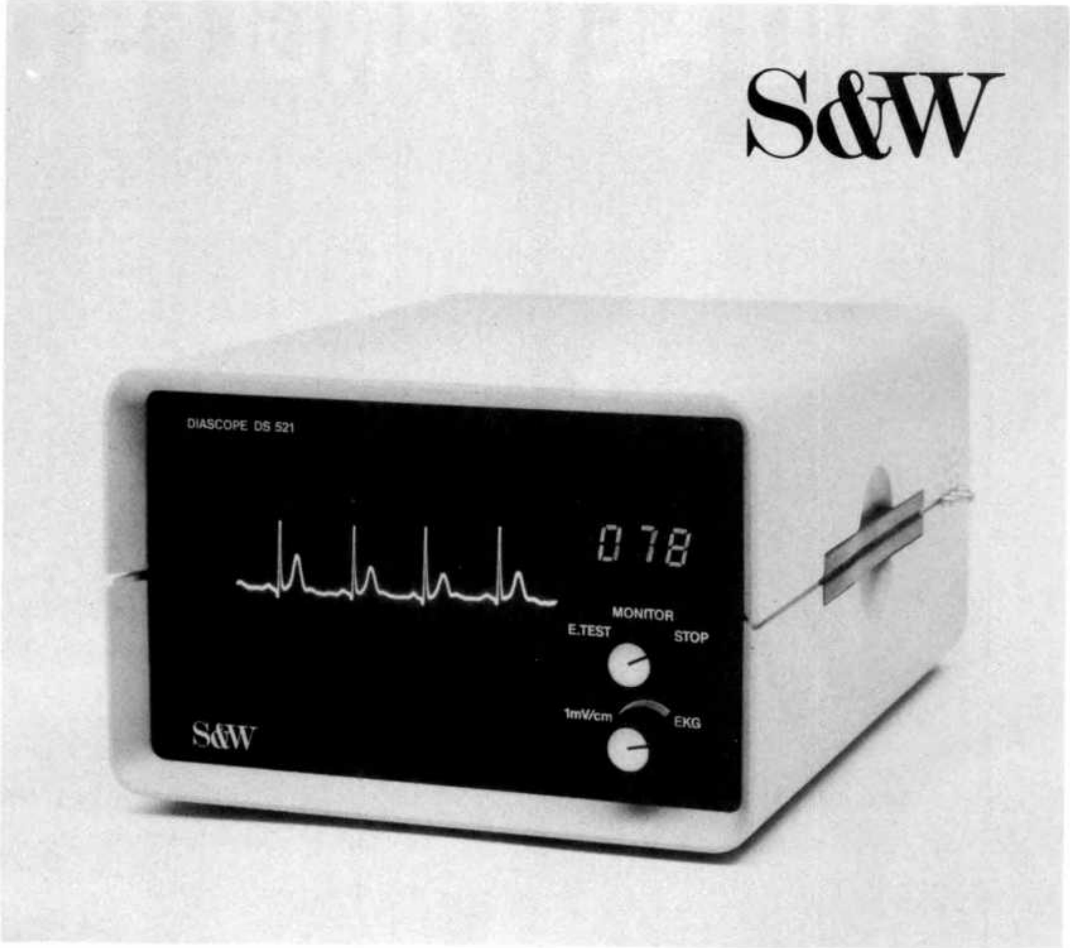

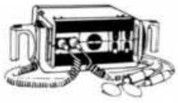
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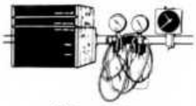
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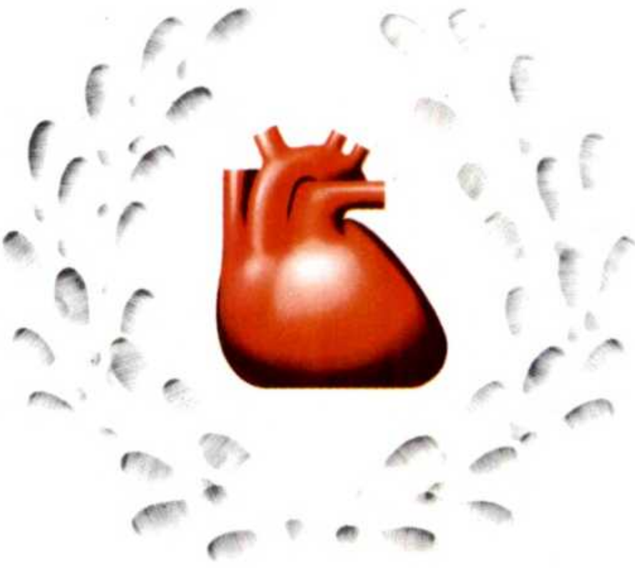

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Recurring cardiac myxoma

IAN R GRAY, W G WILLIAMS

From the Walsgrave Hospital, Coventry, West Midlands

SUMMARY Of a series of 14 patients surviving operation for atrial myxoma, two developed signs of recurrence of the tumour. In both cases the patients underwent two further separate operations for recurrent lesions. The time before the second recurrence was nearly 11 years and four and a half years. In neither case did histological examination show malignant change.

These two cases of recurrent atrial myxoma, together with four other reported cases, indicate that a second recurrence may occur in about 25% of patients with a first recurrence. Multiple foci of tumour growth is probably the explanation for recurrence in most cases.

Myxoma is the only primary tumour of the heart to occur with any frequency. It arises from the endocardium, usually of the atrial septum, and grows into the left or right atrial cavity. Seventy five per cent of myxomas are in the left atrium, 20% in the right atrium, and the remainder in one or other ventricle. It began to be recognised in life in patients undergoing mitral valvotomy and could be visualised by angiocardiography. Echocardiography has greatly improved the promptness and the accuracy of clinical diagnosis. Crafoord in 1954 was the first to remove successfully a left atrial myxoma.[1] With open heart techniques surgical treatment has become safe and effective.

It was in 1967, several years after surgical treatment became widely practised, that Gerbode *et al* encountered the first recurrence.[2] They thought it occurred because the tumour had not been completely removed at the first operation and recommended wide resection of the atrial septum around the point of origin of the tumour. Read *et al* reported, however, a patient with recurrence after a myxoma had been removed with excision of the septum around its origin.[3] The recurrent tumour arose from the atrial wall, not the site of the original myxoma. Jugdutt *et al* stressed that five of the nine recurrences then recorded in published reports had happened despite wide resection and patching of the atrial septum.[4] Their patient had a recurrence two and a half years after the original myxoma was excised. When he died four years later there were no less than six myxomas in the left atrium, one of which extended through the septum to the right atrium. There are three other reports of myxoma recurring for a second time.[3 5 6] In one of them, O'Neil *et al* reported a patient who developed a recurrent myxoma on the annulus of the tricuspid valve four years after a left atrial myxoma was removed and a further recurrence in the right atrium eight years later.[5] They emphasise that each recurrence was "upstream" from the one before and unlikely, therefore, to be caused by seeding from an earlier lesion.

Cleveland *et al* reported a patient who had a myxoma removed from the posterior wall of the left atrium.[6] It recurred at the same point on the atrial wall. A second recurrence took place when there was a tumour on the posterior wall of the atrium together with multiple smaller myxomas elsewhere in the left atrium. They described the cellular pattern of the tumour as "more aggressive" with each recurrence, the second recurrence being malignant.

We report two further cases of repeated recurrence of myxoma which we have encountered in a total experience of 15 patients with atrial myxoma, 14 of whom were operated on successfully.

Patients and methods

CASE REPORTS

Case 1

A 42 year old woman had suddenly developed severe pain in the left leg at the age of 18 years and was admitted to hospital for a few days in 1960. Six months later she again entered hospital with fatigue, breathlessness, and haemoptysis. There were presys-

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tolic and systolic murmurs at the mitral area, the chest radiograph showed pulmonary congestion, and she was profoundly anaemic. She was thought to have rheumatic carditis and responded to steroid treatment. She relapsed a few weeks later and again entered hospital, being admitted this time to a different ward. The ward sister remembered having looked after her sister two years earlier, when she died of a left atrial myxoma. This information resulted in a reappraisal of her condition, when it was found that there were no arterial pulses below the femoral arteries in either leg. Pulmonary angiography showed a filling defect in the left atrium. In May 1961, under surface cooling, the left atrium was opened and a large myxoma removed. No attempt was made to resect the atrial septum around its point of origin, which was in the region of the fossa ovalis. She made a good recovery apart from bilateral intermittent claudication, which gradually disappeared, and occasional paroxysmal tachycardia. She later had two uneventful pregnancies.

In October 1972, she developed pain and discoloration of the right forearm and hand followed by claudication in the arm. Again there were systolic and diastolic murmurs at the mitral area. Pulmonary angiography showed a filling defect in the left atrium. In April 1973, during exploration of the right atrium under cardiopulmonary bypass, a small myxoma was found, which arose from the fossa ovalis. After this had been widely excised a second large filamentous myxoma was removed from the left atrium. The origins on the atrial septum of the two tumours were quite separate from one another. They were both removed together with a cuff of normal septum from around their origins and the septum repaired with a patch of Teflon. The completeness of the excision was confirmed by examining blocks of tissue taken from the excised portions of the atrial septum. She again made a good recovery apart from occasional paroxysmal tachycardia.

Early in 1984 she became unwell with dyspnoea on moderate exertion and a sense of profound malaise. She was quite certain that the myxoma had recurred. There was a long systolic murmur at the left sternal edge and suspicious echoes in the neighbourhood of the tricuspid valve on M mode echocardiography. At cardiac catheterisation there was a pronounced diastolic gradient across the tricuspid valve. Right atrial angiocardiography showed a large lobulated filling defect closely related to the ventricular aspect of the tricuspid valve. At her third operation, in February 1984, we found an enormous myxoma which occupied most of the right ventricular cavity. It had multiple points of attachment to the papillary muscles, and to remove it completely the tricuspid valve had to be excised. There was a second small myxoma in the left atrium which arose from the endothelium covering the Teflon patch previously placed in the atrial septum. This also was removed. She developed atrial flutter a few days later which required DC cardioversion.

The histology of the tumours removed at all three operations was that of benign myxoma with no suggestion of malignant change.

Case 2

A 47 year old man had collapsed with loss of consciousness and slurred speech in 1961 when he was 23 years old. We found no cause for this attack. Two years later he developed a right hemiparesis and focal epilepsy. Left carotid and vertebral arteriograms in 1964 showed what were described as multiple angiomata in the left hemisphere, two previous carotid studies having been normal. At the time we believed this to be a primary vascular condition, but with hindsight the appearances closely resembled those subsequently reported in patients with cerebral embolus from left atrial myxoma.[7–9] In 1970, nine years after the first cerebral symptoms, he had a femoral embolus. Histology of the material removed at embolectomy showed the typical appearances of myxoma. There were no cardiac symptoms and no abnormal signs in the heart. Intracardiac pressures were normal, but pulmonary angiography showed a filling defect in the left atrium. In June 1970 a myxoma 5 cm in diameter was removed from the left atrium together with its pedicle and an area of septum around its base. We repaired the septum by direct suture. He developed atrial flutter afterwards which required DC cardioversion.

Fifteen months later he was taken ill with fever, breathlessness, slurred speech, and hyperaesthesia of the right side of the body. He had atrial fibrillation and pronounced pulmonary oedema. Pulmonary angiography showed a large filling defect in the left atrium. At operation in September 1971 we found a myxoma which arose from the atrial septum and which completely filled the left atrium. We removed the tumour together with the atrial septum around its point of origin, which was repaired with a patch of Teflon. Examination of blocks of the septal tissue confirmed that removal had been complete.

He remained well until December 1975 when he suddenly lost consciousness with Adams-Stokes syncope. There was second degree heart block with Wenkebach phenomenon, and the ventricular complex showed right bundle branch block with left posterior fascicular block. These conduction abnormalities resolved spontaneously. There were no abnormal signs on auscultation, and an M mode echocardiogram was normal. Angiocardiography showed a filling defect in the left atrium and another

Table 1 *Incidence of recurrence of atrial myxoma*

Authors	*No of cases surviving operation*	*Recurrences*
Gerbode *et al* (1967)[2]	7	1
Croxson *et al* (1977)[11]	9	0
Kabbani and Cooley (1973)[12]	17	1
Chassignolle *et al* (1973)[13]	10	1
Puel *et al* (1973)[14]	5	1
Hardin *et al* (1974)[15]	12	1
Sasaki *et al* (1977)[16]	9	1
O'Neil *et al* (1979)[5]	5	1
Donahoo *et al* (1979)[17]	14	0
Bulkley and Hutchins (1979)[18]	12	0
Richardson *et al* (1979)[19]	11	0
Attar *et al* (1980)[20]	6	1
St John Sutton *et al* (1980)[10]	39	2
Cleveland *et al* (1983)[6]	15	1
Marvasti *et al* (1984)[21]	9	0
Present series (1985)	14	2
Total No (%)	194	13 (7)

in the right ventricle. At a third operation in February 1976, there was a large myxoma of the right atrium together with two small ones, a large myxoma of the right ventricle that affected the tricuspid valve, a myxoma in the left atrium which arose from endothelium covering the Teflon patch, and a further myxoma in the main pulmonary artery which extended into the left pulmonary artery. All six myxomas were removed; the tricuspid valve was replaced, and a permanent pacing system implanted. He remained well eight years later. The histology of the tumour tissue removed at the three operations showed only the appearances of benign myxoma.

Discussion

The largest series of patients with myxoma operated on in a single centre is that reported from the Mayo Clinic.[10] Two out of 39 patients who survived operation had recurrence, an incidence of 5·4%. This may be an underestimate as half of their patients had been followed for less than 10 years. When 16 series of cases of atrial myxoma are added together, totalling 194 patients who survived operation, there were 13 with recurrence, an incidence of 7% (Table 1).

We have found reports of 21 patients whose myxoma recurred after surgical treatment, to which we have added the present two cases above (Table 2). Their ages ranged from 5 to 59 years at the first operation. The sex was recorded in only 13 of the 23; nine of the 13 were male. This is surprising since primary myxoma occurs much more often in women than in men. The original myxoma was in the left atrium in every case, and in 14 the recurrence also was a single tumour in the left atrium. The recurrent tumour was in the right ventricle in one case, in another it involved the chordae and a cusp of the mitral valve, and in another it was on the tricuspid valve. There was more than one tumour in the other six patients: four had two or more tumours in the left atrium and two had recurrence in both left and right atrium. Recurrence has usually been within four years of the first operation (19 out of 23), but in our first case more than 10 years elapsed before the first recurrence, and in another it was not detected until 14 years after the first tumour was removed.[13]

Table 2 *Reported cases of recurrent myxoma*

Authors	*Age (yr)/sex*	*Site of primary myxoma*	*Time of recurrence*	*Site of recurrence*
Gerbode *et al* (1967)[2]	—	LA	4 yr	LA
Bahl *et al* (1969)[22]	34/F	LA	6 yr 5 mnth	LA
Walton *et al* (1972)[23]	—	LA	1 yr 10 mnth	LA, RA
Kelly and Bhagwat *et al* (1972)[24]	—	LA	7 mnth	LA
Kabbani and Cooley (1973)[12]	19/F	LA	1 yr 5mnth	LA (4)
Mussini-Montpellier *et al* (1973)[25]	5/M	LA	2 yr	LA
Puel *et al* (1973)[14]	15/M	LA	1yr 2 mnth	LA (2)
Chassignolle *et al* (1973)[13]	—	LA	14 yr	LA
Maranhao *et al* (1973)[26]	—	LA	3 yr 8 mnth	LA
Read *et al* (1974)[3]	39/M	LA	7 mnth	Mitral valve
	59/M	LA	1 yr 3mnth	LA*
Hardin *et al* (1974)[15]	—	LA	2 yr 6 mnth	LA
Zackai *et al* (1974)[9]	47/M	LA	1 yr 7mnth	LA
Jugdutt *et al* (1975)[4]	46/M	LA	2 yr 6 mnth	LA (2)*
Dang and Hurley (1976)[27]	22/M	LA	3 yr 7 mnth	RV
Sasaki *et al* (1977)[16]	—	LA	8 mnth	LA (multiple)
O'Neil *et al* (1979)[5]	18/M	LA	4 yr	Tricuspid valve*
Attar *et al* (1980)[20]	—	LA	—	LA
St John Sutton *et al* (1980)[10]	—	LA	<3 yr	LA
	—	LA	<3 yr	LA
Cleveland *et al* (1983)[6]	—	LA	<4 yr	LA*
Present series (1985)				
Case 1	19/F	LA	11 yr 11 mnth	LA, RA*
Case 2	32/M	LA	1 yr 3 mnth	LA*

LA, left atrium; RA, right atrium; RV, right ventricle.
*Cases having a second recurrence (Table 3).

Table 3 *Repeated recurrence of cardiac myxoma*

Author	*Sex/age (yr) at first operation*	*Site of original myxoma*	*Time to first recurrence*	*Site of first recurrence*	*Time to second recurrence*	*Site of second recurrence*
Read *et al* (1974)[3]	M/59	LA	1 yr 3 mnth	LA	7 mnth	LA (2)
Jugdutt *et al* (1975)[4]	M/46	LA	2 yr 6 mnth	LA (2)	3 yr 6 mnth	LA (6), RA
O'Neil *et al* (1979)[5]	M/18	LA	4 yr	Tricuspid valve	4 yr	RA
Cleveland *et al* (1983)[6]	F/48	LA	<4 yr	LA	<4 yr	LA (multiple)
Present series (1985)						
Case 1	F/19	LA	11 yr 11 mnth	LA, RA	10 yr 10 mnth	RV, tricuspid valve, LA
Case 2	M/32	LA	1 yr 3 mnth	LA	4 yr 5 mnth	LA, RV, PA, RA (3)

LA, left atrium; RA, right atrium; RV, right ventricle; PA, pulmonary artery.

Four of the six patients in whom myxoma recurred for a second time were men (Table 3). The time that elapsed between the first and second recurrence was less than five years in five of the six, the time in the sixth (our case 1) being nearly 11 years. The six cases of a second recurrence of myxoma indicate that it is likely to occur in about 25% of patients in whom a first recurrence has taken place. There was more than one tumour at the second recurrence in five of the six, more than one chamber being involved in three of them.

Incomplete removal of a myxoma at the first operation might explain a few of the recurrences, especially when the operation had to be carried out hurriedly under hypothermia as in our first patient. Most of the recurrences, however, have followed more leisurely procedures using cardiopulmonary bypass, with wide excision of the atrial septum around the point of origin of the tumour. Recurrences have also occurred at a different site, even in a different cardiac chamber, from the first myxoma. One of the recurring tumours in each of the present cases actually arose from endothelium covering a Teflon patch in the atrial septum. Read *et al* suggested that implantation of tumour tissue from the primary myxoma might be responsible for some recurrences.[3] This could happen either at operation or from damage to a large myxoma forced into the orifice of the mitral valve during atrial systole. This could explain only recurrences that were in the wall of the left atrium or in the mitral valve.

It is also possible that the recurrent tumours are quite distinct from the original myxoma and are the result of multiple foci of neoplastic change. The several reports of simultaneous development of more than one cardiac myxoma favour this hypothesis. Nichols and Hennigar describe postmortem findings in a young woman who had one large and five small myxomas in the left atrium and another small myxoma in the right atrium.[28] All these seven myxomas had separate origins on the atrial septum. Other cases of multiple cardiac myxomas were reported by Frankenfeld *et al* and Zajtchuk *et al*.[29 30] There may also be a genetic factor in the multiple incidence of myxoma. Siltanen *et al* reported a patient who underwent surgery for myxomas that had developed simultaneously in both atria.[31] Three of her seven children also developed atrial myxoma. Our first patient with two recurrences of myxoma also had a familial incidence of the condition.

Although myxoma is generally regarded as a benign tumour, there are reports of tumour emboli of myxoma that have behaved in a malignant fashion. A patient reported by Read *et al* had a secondary growth on the sternum some years after a left atrial myxoma was removed: a biopsy specimen was reported as showing myxosarcoma.[3] In the case reported by Heath and Mackinnon there were multiple myxomatous infarcts in the lungs from a right atrial myxoma.[32] In some of these embolic lesions myxomatous tissue had invaded the media of the pulmonary arteries. Similar invasion of the wall of the cerebral arteries in myxomatous cerebral embolism was reported by New *et al*.[7] The histology of myxomas recurring in the heart has not usually suggested malignant change, nor has the histology of tumours which have recurred seemed in any way different from non-recurring myxoma. In only one case (Cleveland *et al*), where myxoma recurred twice in the left atrium, was there progression of the histological appearance from benign to malignant.[6]

Weighing up the four possible causes of recurrence—incomplete removal, seeding of tumour, multiple foci of tumour development, and malignant change—we believe that multiple foci of tumour growth best explain the condition in most cases. A few cases might recur because of incomplete removal of the primary tumour, but this cannot possibly explain all the features of the recurring myxomas we have described. Malignant change has been recognised in the tumour histology in only one of the reported cases. The association of multiple tumours with a familial incidence of myxoma is an interesting feature, and the difference in the sex incidence of primary and recurring myxomas is an aspect which remains unexplained.

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Case reports

Hypoplastic left heart with complete transposition of the great arteries

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SUMMARY A male newborn infant with hypoplastic left heart and transposition of the great arteries died on the second day of life. The haemodynamic consequences of this malformation are considerably different from those of ordinary hypoplastic left heart syndrome because of pulmonary rather than aortic atresia. In the absence of cross sectional echocardiographic equipment, cardiac catheterisation with angiography is necessary to delineate the anatomical picture. These two conditions have not apparently been reported before in association.

Hypoplastic left heart syndrome is defined clinically as severe underdevelopment of the left ventricle and atresia of the aortic or the mitral valve or both.[1] The incidence of this malformation accounted for 1·5% of 15 105 cases of congenital heart defects.[2] To our knowledge hypoplastic left heart syndrome in combination with complete transposition of the great arteries has not been previously reported.[2 3] We report a male infant with this malformation.

Case report

A male infant was born after an uneventful pregnancy and delivery (birth weight 3·81 kg). He was transferred to our hospital several hours after birth because of progressive cyanosis and tachypnoea. Physical examination also showed a slightly accentuated precordial impulse and a normal first and a single second heart sound. A short systolic murmur (grade 2/6) was heard along the left sternal edge. The liver edge was palpable 3 cm below the right costal margin, and the brachial and femoral artery pulses were normal.

INVESTIGATIONS

The electrocardiogram showed right axis deviation and right ventricular hypertrophy with a net negative deflection over the left precordium. The chest radiograph showed an enlarged heart and reduced pulmonary vasculature. The liver was on the right and the stomach on the left side.

Echocardiography—The M mode echocardiogram (Fig. 1a) showed hypoplasia of the posterior (left) ventricle (left ventricular end diastolic dimension <10 mm), a hypoplastic posterior (mitral) atrioventricular valve, an enlarged anterior (tricuspid) atrioventricular valve, and an enlarged anterior (right) ventricle. There was also a large anterior vessel arising from the anterior ventricle and a small posterior vessel overriding the ventricular septum but without access to either of the two ventricles. The suprasternal notch view indicated that the hypoplastic vessel was the pulmonary artery. This interpretation was confirmed subsequently by cardiac catheterisation and angiography.

Haemodynamic data—There was systemic pressure in the right ventricle and no gradient to the ascending aorta (Table). The oxygen saturation percentages indicated an interatrial left to right shunt.

Angiography of the left atrium, right ventricle, and the ascending aorta showed a small left atrium and an intense backflow of contrast medium into the pulmonary veins. The left ventricle was not opacified (Fig. 1b). Instead the contrast medium passed from the left to the right atrium and hence into the right ventricle, from which opacification of the anteriorly placed ascending aorta occurred. A hypoplastic pulmonary artery was filled from the distal aortic arch through a

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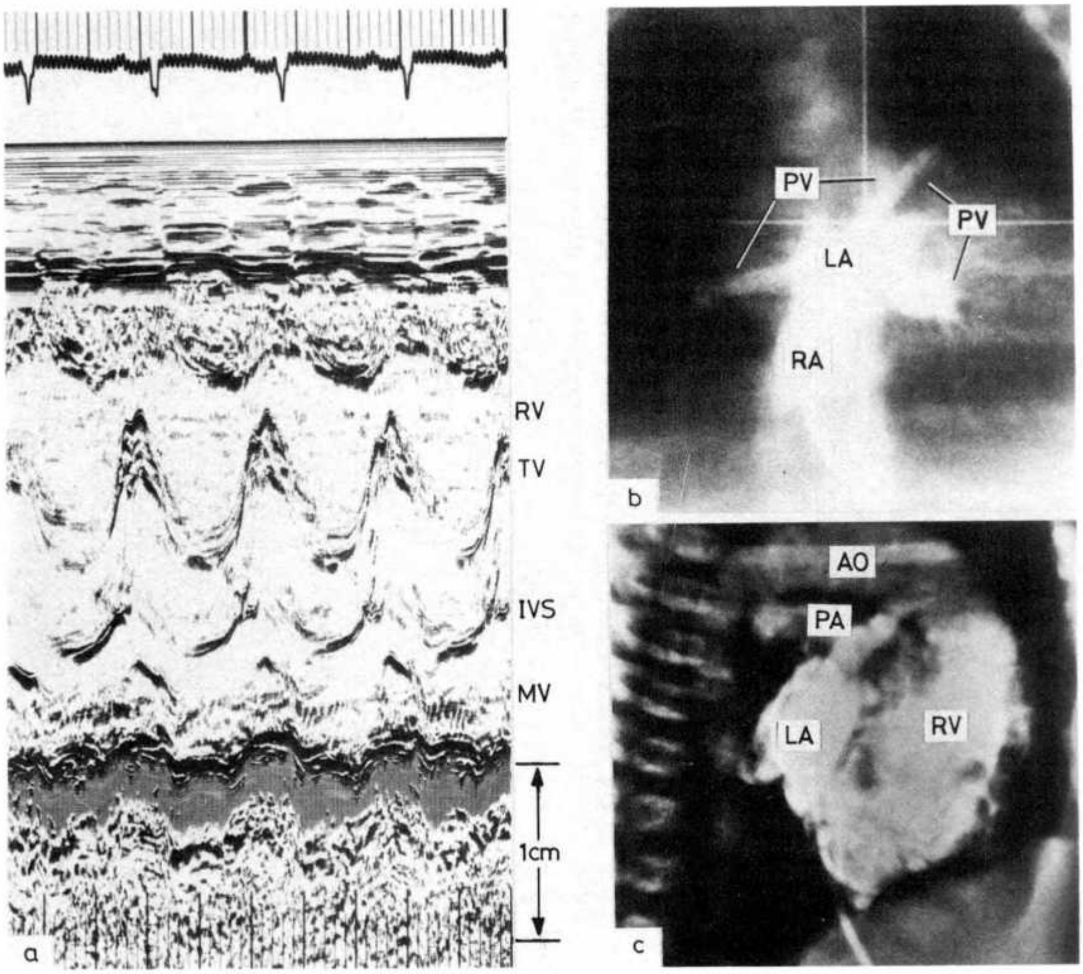

Fig. 1 *(a) M mode echocardiogram in parasternal view showing hypoplasia of the posterior (left) ventricle (left ventricular end diastolic dimension <10 mm), a hypoplastic posterior (mitral) valve (MV), and an enlarged anterior (right) ventricle (RV) and tricuspid valve (TV). IVS, interventricular septum. (b) Left atrial angiogram in the anteroposterior view showing filling of the left atrium (LA) and the pulmonary veins (PV) and reflux of contrast media into the right atrium (RA); there was no opacification of a left ventricle. (c) Left atrial angiogram in the lateral projection showing opacification of the left atrium (LA), filling of the right ventricle (RV) by a left to right interatrial shunt, and a discordantly connected aorta (AO). Opacification of the hypoplastic posterior pulmonary artery (PA) occurred via a persistent ductus arteriosus.*

small ductus arteriosus (Fig. 1c).

Diagnosis—Situs solitus with atrioventricular concordance and ventriculoarterial discordance (complete transposition of the great arteries), atresia of the mitral (imperforate valve) and pulmonary valves, hypoplasia of the left ventricle, and a patent foramen ovale were diagnosed.

Necropsy—The patient died on the second day of life. The diagnosis was confirmed at necropsy. The left atrioventricular valve was imperforate and the valve annulus small. The left ventricle was a slit like

Table *Haemodynamic data*

Site	*Pressure (mean) (mm Hg)*	*Oxygen saturation (%)*
Superior vena cava	—	30
Mid right atrium	7/0 (1)	43
Inferior vena cava	—	36·5
Right ventricle	80/0 (10)	40
Ascending aorta	80/50 (63)	42
Left atrium	11/0 (2·5)	95

Systemic blood flow 8·3 l/min m^2.
Pulmonary blood flow 1·2 l/min m^2.
Effective pulmonary blood flow = 1·1 l/min m^2.

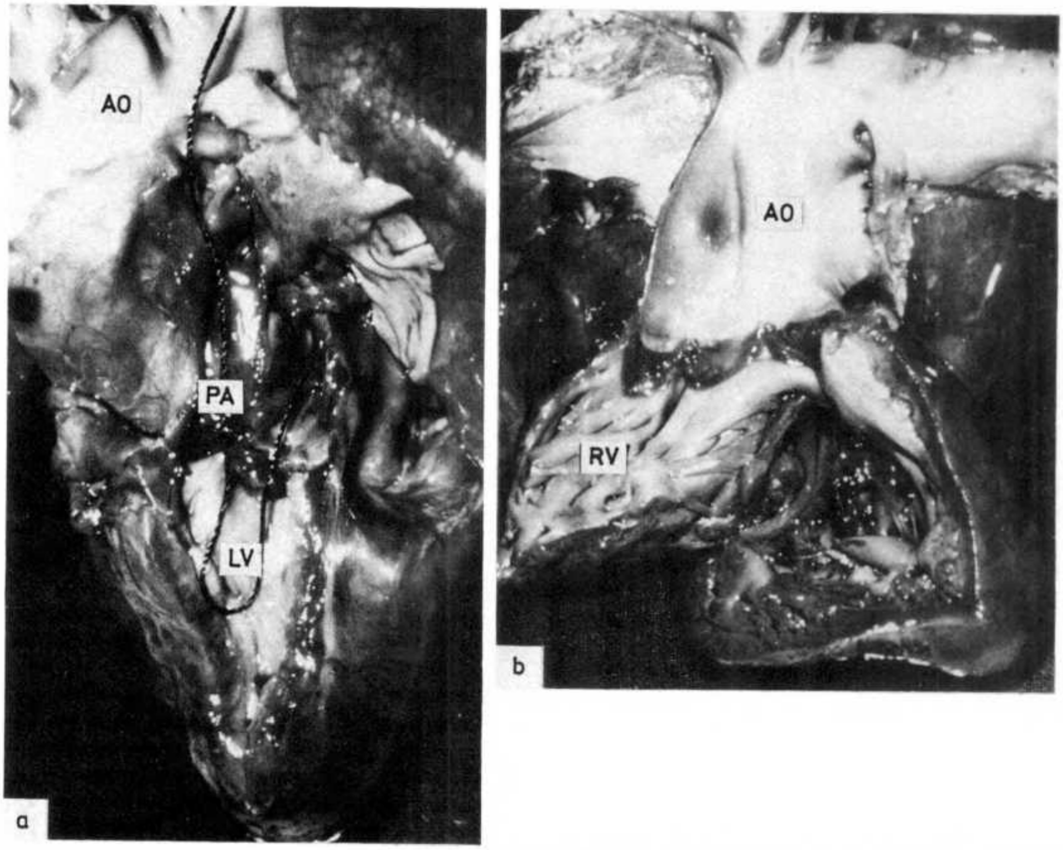

Fig. 2 *Morphological appearance of (a) the hypoplastic left ventricle (LV) and the pulmonary artery (PA) and (b) the enlarged grossly trabeculated right ventricle (RV) giving rise to a large aortic root.*

chamber, which showed a typical left ventricular morphology with smooth trabeculation. There was no endocardial fibroelastosis (Fig. 2a). The pulmonary valve consisted of three leaflets which were fused at their commissures, thus forming an imperforate valve. The valve ring and the pulmonary trunk were hypoplastic up to the bifurcation. The right ventricle was enlarged and showed gross trabeculation. The wide aortic root was connected to a non-restrictive right ventricular infundibulum, and the aortic valve leaflets were tricuspid and not stenotic (Fig. 2b). The right coronary artery originated from the posterior sinus and the left from the left sinus of the aortic valve. The foramen ovale was patent and the ductus arteriosus persisted. No other associated anomalies were found.

Discussion

To our knowledge hypoplastic left heart syndrome with transposition of the great arteries has not previously been reported.[2,3] One case of aortic artresia in association with complete transposition of the great arteries but without hypoplastic left ventricle and mitral atresia has been reported.[4] Transposition, ventricular septal defect, and severe pulmonary stenosis or atresia occur in about 5% of neonates with transposition.[5]

The haemodynamic consequences of this malformation are considerably different from those of the ordinary hypoplastic left heart syndrome with regard to the blood supply to the systemic and the pulmonary circulations. The physiology, of course, is also different from that in simple transposition of the great arteries and resembles that in univentricular heart with pulmonary atresia. The physical and radiographic findings (normal pulses and diminished pulmonary vasculature) do not therefore suggest hypoplastic left heart syndrome. The electrocardiogram and the M mode echocardiogram may indicate left heart hypoplasia but are not reliable in detecting ventriculoarterial discordance. With echocardiography, however, an imperforate atrioventricular valve may be differentiated from an absent connection.[6] With cross sectional echocardiography a correct diagnosis may also be established without major difficulty. In the absence of cross sectional echocardiographic equipment, cardiac catheterisation with angiocardiography is necessary to delineate the anatomical picture.

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Br Heart J 1985; 53: 654–8

Ventricular tachycardia induced by clonidine withdrawal

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SUMMARY Ventricular tachycardia developed after the abrupt withdrawal of clonidine in a patient with atrial septal defect of the ostium secundum type, renal insufficiency, and hypertension. Ventricular tachycardia was completely suppressed by intravenous phentolamine, which contrasted with the limited effectiveness of intravenous lignocaine and procainamide. Sublingual glyceryl trinitrate or inhaled amyl nitrate reduced the blood pressure to a level similar to that after phentolamine but had no effect on the ventricular tachycardia. Ventricular tachycardia was probably produced by humoral or neural stimulation, or both, of upregulated myocardial alpha adrenoceptors.

It is known that the abrupt withdrawal of clonidine hydrochloride (clonidine) is often associated with a syndrome characterised by excessive efferent sympathetic activity producing raised serum catecholamine concentrations and clinical manifestations similar to those in pheochromocytoma.[1–4] Although frequent atrial and ventricular extrasystoles have been reported,[1] serious ventricular arrhythmias are rare in the clonidine withdrawal syndrome. To our knowledge, only one case of ventricular fibrillation has been reported 12 hours after the withdrawal of clonidine during aortocoronary bypass surgery.[2]

We report a patient with atrial septal defect of the ostium secundum type, chronic renal failure, and hypertension, who experienced paroxysmal ventricular tachycardia two days after stopping oral clonidine.

Case report

A 60 year old woman with atrial septal defect had an eight year history of hypertension and intermittent pretibial oedema. Her blood pressure was 165/105 mm Hg, and she was treated with 0·45 mg clonidine daily. One month later her blood urea nitrogen concentration was 18·9 mmol/l (53·0 mg/100 ml) and serum creatinine concentration 203 mmol/l (2·3 g/100 ml). She was admitted to our clinic for further evaluation of progressive oedema eight months later. Two days before admission she had stopped taking clonidine (Fig. 1).

On admission, her height was 148 cm, weight 46 kg, body temperature 36·3°C, and blood pressure 130/80 mm Hg. No cyanosis was noticed. The jugular veins were slightly distended and minimal pretibial pitting oedema was present. The pulse was irregular at a rate of 120 beats/min, the respiratory rate was 18/min, and a grade 3/6 early systolic murmur was heard most clearly in the third intercostal space at the left sternal border. The two components of the second heart sound were widely separated, which was confirmed by a phonocardiogram. The resting electrocardiogram showed normal sinus rhythm with paroxysmal ventricular tachycardia (Fig. 2a) and inverted T waves in the precordial leads.

A chest radiograph showed increased pulmonary markings, a pronounced convexity of the cardiac shadow to the right of the sternum, a normal sized aortic knuckle, and a prominent pulmonary knuckle. M mode and cross sectional echocardiograms showed an enlarged right ventricle, paradoxical motion of the interventricular septum, a narrow left ventricular outflow tract, and a high D point of the mitral valve.

Serum sodium concentration was 148 mmol/l, potassium 4·9 mmol/l, chloride 111 mmol/l, bicarbonate 16·2 mmol/l, calcium 77 mg/l, phosphorus 62 mg/l, lactate dehydrogenase activity 564 IU/l, serum aspartate aminotransferase activity 46 IU/l, serum alanine aminotransferase activity 48 IU/l, and creatine phosphokinase activity 131 IU/l. Packed cell volume was 36·8%, haemoglobin 11·8 g/dl, red blood cell count 4·13 × 10^{12}/l, and white blood cell

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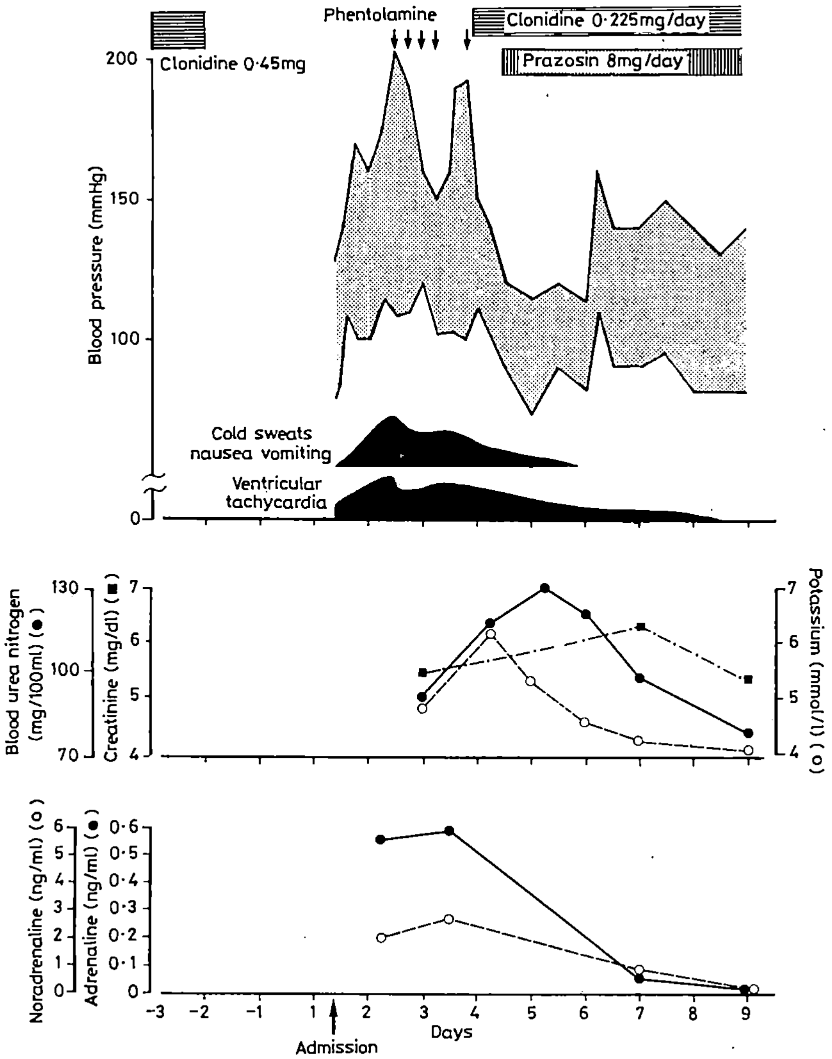

Fig. 1 *Relation between blood pressure, blood urea nitrogen concentration, serum creatinine concentration, serum potassium concentration, and adrenaline and noradrenaline concentrations and administration of phentolamine, prazosin, and clonidine.*

Conversion: SI to traditional units–urea nitrogen: 1 mmol/l ≈ 2·8 mg/dl; creatinine: 1 μmol/l ≈ 0·01 g/dl; adrenaline: 1 ng/100 ml ≈ 0·054 nmol/l; noradrenaline 1 ng/100 ml ≈ 0·059 nmol/l.

count 6·9 × 10^9/l. Blood urea nitrogen concentration was 32 mmol/l (90·2 mg/100 ml), creatinine 486 μmol/l (5·5 mg/100 ml) and calculated creatinine clearance 9·24 ml/min. Urine analysis showed 400 mg/l of protein.

Blood pressure rose gradually to 220/120 mm Hg by midday of the second hospital day (Fig. 1). Nausea, vomiting, and cold sweats developed concomitantly, and the intervals between episodes of paroxysmal ventricular tachycardia were shorter (Fig. 2b). Serum adrenaline and noradrenaline concentrations appreciably increased (3·2 nmol/l (0·59 ng/ml) and 15·6 nmol/l (2·64 ng/ml) respectively) (Fig. 2c), and a diagnosis of clonidine withdrawal syndrome was made.

Intravenous lignocaine 100 mg and procainamide 200 mg failed to suppress the ventricular tachycardia completely. Nevertheless, an intravenous injection of 10 mg phentolamine completely suppressed ventricular tachycardia within two minutes with a decrease in blood pressure and pronounced symptomatic improvement (Figs. 2b and c). Repeated doses of phentolamine achieved similar results, while serum catecholamine concentrations were unchanged by phentolamine after 30 minutes (Fig. 2c). To examine the effects of the fall in blood pressure and afterload reduction of arrhythmias, we gave glyceryl trinitrate or amyl nitrate. Sublingual glyceryl trinitrate 0·3 mg decreased arterial pressure from 196/106 mm Hg to 170/102 mm Hg, and the inhalation of amyl nitrate

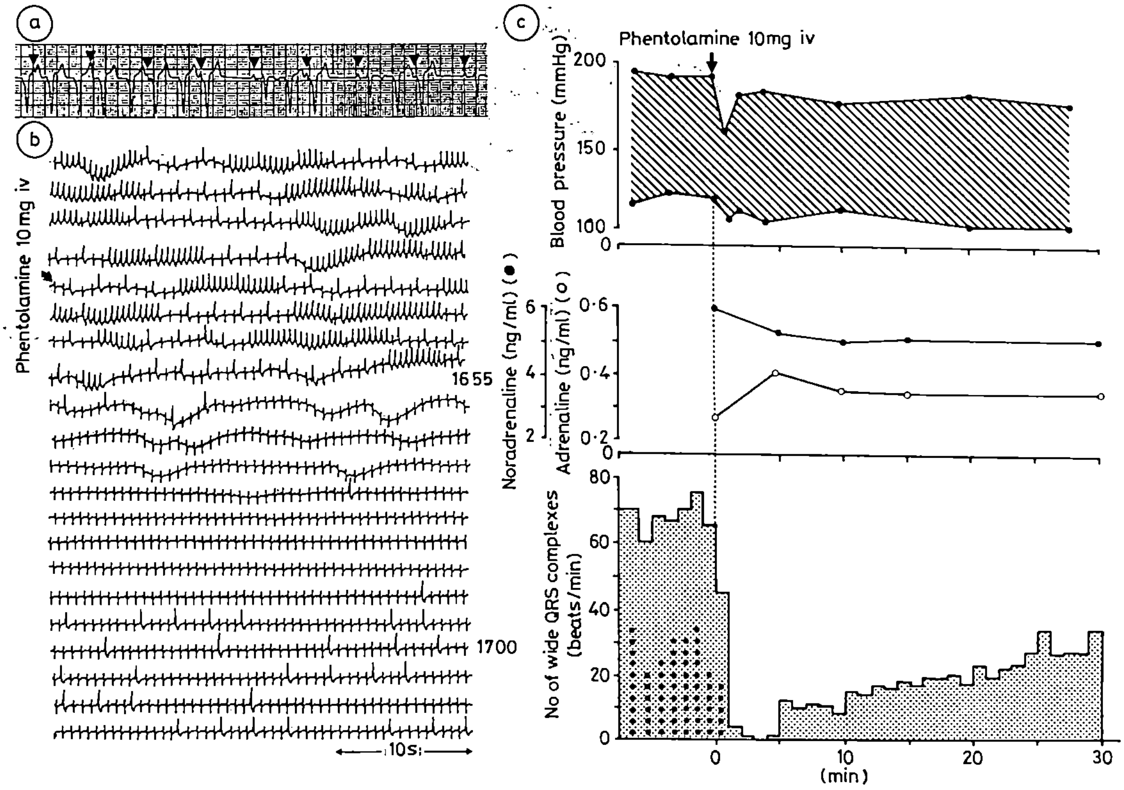

Fig. 2 *(a) Electrocardiogram (lead V2) (▼ denotes P ware), (b) continuous electrocardiogram (lead CM5) before and after intravenous phentolamine, and (c) chronological changes in blood pressure, serum adrenaline, and noradrenaline concentrations, and frequency of wide QRS complexes (● denotes number of episodes of ventricular tachycardia (>3 consecutive wide QRS complexes)) before and after intravenous phentolamine. Repetitive runs of ventricular tachycardia were recorded and were suppressed completely two minutes after intravenous phentolamine.*

Conversion: SI to traditional units—adrenaline: 1 ng/100 ml ≈ 0·054 nmol/l; noradrenaline 1 ng/100 ml ≈ 0·059 nmol/l.

from 184/116 mm Hg to 160/106 mm Hg. Neither agent, however, affected the occurrence or frequency of episodes of ventricular tachycardia.

Renal function progressively deteriorated after admission, with the blood urea nitrogen concentration rising to 46·4 mmol/l (130 mg/100 ml) and potassium concentration to 6·2 mmol/l. We began treatment with 0·225 mg clonidine and 8 mg prazosin daily on the third and fourth hospital day respectively, which lowered the blood pressure to 120/90 mm Hg within 12 hours and symptoms subsided within 48 hours. The number of episodes of ventricular tachycardia decreased gradually, and the arrhythmia did not recur after the ninth hospital day (Fig. 1). The concentrations of blood urea nitrogen, creatinine, and serum potassium fell to the values before admission on the ninth hospital day.

The clinical course was uneventful with treatment until two months later, when she developed severe headaches with neck rigidity. She collapsed suddenly and cardiopulmonary resuscitation was unsuccessful. Necropsy showed a massive subarachnoid haemorrhage secondary to rupture of an aneurysm of the left anterior communicating artery, a large ostium secundum defect, and chronic glomerulonephritis. No evidence of pheochromocytoma or significant coronary atherosclerosis was found.

Discussion

In our patient, in whom paroxysmal ventricular tachycardia occurred after abruptly stopping clonidine, the arrhythmia was probably a manifestation of clonidine withdrawal since it occurred in conjunction with other clinical evidence of this syndrome including raised serum catecholamine concentrations. Furthermore, intravenous phentolamine or oral clonidine (the usual therapeutic drugs for the clonidine withdrawal syndrome) was more effective in controlling ventricular tachycardia than other regularly used antiarrhythmic agents.

The mechanism of ventricular tachycardia associated with clonidine withdrawal is unknown. Nevertheless, there are several possible theories. Firstly, high blood pressure is known to aggravate catecholamine induced arrhythmias.[5] The effectiveness of phentolamine in suppressing ventricular tachycardia in this patient might have been due to the accompanying fall in blood pressure. This possibility is, however, unlikely since sublingual glyceryl trinitrate or inhaled amyl nitrate, sufficient to reduce blood pressure to the level similar to that after phentolamine, had no effect on ventricular tachycardia.

Secondly, ventricular tachycardia might have been caused by direct stimulation of the myocardial adrenoceptors by circulating catecholamines or cardiac sympathetic nerves. The notable effect of phentolamine on ventricular tachycardia in contrast to the limited effectiveness of the usual antiarrhythmic drugs strongly suggests that alpha adrenergic mechanisms were involved in the genesis of ventricular tachycardia. A beta blocker was not given because of possible worsening of the withdrawal syndrome.[1-4]

Recently, the presence of myocardial alpha receptors has been reported experimentally,[6] and their role in the genesis of some specific cardiac arrhythmias has been clarified. Picrotoxin, a central nervous system stimulant, produces demonstrable ventricular tachyarrhythmias in animals,[7] and these tachyarrhythmias can be suppressed by phentolamine but not by propranolol. These arrhythmias are thought to be caused by stimulation of myocardial alpha receptors by cardiac sympathetic nerves or by circulating catecholamines released from the adrenal gland or both. Cor and Crafford and Sheridan *et al* found alpha blockade to be effective in suppressing ventricular tachyarrhythmias induced by coronary artery reperfusion in cats.[6 8] They found an increased number and affinity of myocardial alpha receptors in this experimental model.[6]

It is likely that sympathetic hyperactivity associated with clonidine withdrawal involves predominantly alpha adrenergic mechanisms since alpha blockers usually relieve the clinical symptoms of clonidine withdrawal, while beta blockers occasionally make them worse.[1-4] Why alpha adrenergic hyperactivity predominates in this syndrome is not known, but it is likely that upregulation of alpha adrenergic receptors occurs after the abrupt withdrawal of clonidine.[4]

Clonidine reduces the release of noradrenaline into the synapse, acting as a presynaptic alpha receptor agonist, and, furthermore, behaves as an alpha adrenergic antagonist postsynaptically. Thus sustained treatment with clonidine results in a loss of noradrenaline-receptor interaction at the synapse with an increase of alpha receptor concentration postsynaptically.[9 10] The abrupt withdrawal of clonidine results in increased efferent sympathetic outflow with enhanced release of catecholamines from the adrenal gland and sympathetic nerve endings.[4] Increased activation of synaptic alpha receptors, which had increased in number or affinity or both, by the enhanced adrenergic stimulus results in a withdrawal syndrome. An increase in the alpha receptors of the ventricular myocardium after long term treatment with clonidine has been reported.[10] In the present case increased sympathetic outflow to the heart and raised serum catecholamine concentrations would have stimulated the increased cardiac alpha receptors and thus induced ventricular tachycardia. The antiarrhythmic action of phentolamine would have been mediated by the inhibition of cardiac alpha receptors.

The antiarrhythmic effect of phentolamine could have been exerted in the central nervous system, but such a mechanism was probably not predominant since phentolamine penetrates the blood-brain barrier poorly, while a bolus injection of 10 mg phentolamine was sufficient to suppress ventricular tachycardia within two minutes. It is not likely that the minor quinidine like antiarrhythmic action of phentolamine[11] played an important role in our case, since other regularly used antiarrhythmic agents with quinidine like action were not as effective as phentolamine.

Our case was complicated by chronic glomerulonephritis with renal insufficiency, long standing hypertension, and atrial septal defect, which might have predisposed to ventricular tachycardia. Renal insufficiency would have resulted in a high blood concentration of clonidine and led to the withdrawal syndrome since clonidine is excreted mainly by the kidney.[3]

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Resolution of right atrial thrombus shown by serial cross sectional echocardiography

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SUMMARY A 78 year old woman with congestive cardiac failure developed pulmonary embolism. Cross sectional echocardiography detected an undulating fusiform mass attached to the lateral wall of the right atrium and protruding through the tricuspid valve. Serial cross sectional echocardiograms showed a reduction in the size of the mass, and by three months the mass was immobile and attached by a broad base to the lateral atrial wall. The mass was assumed to be a thrombus, and treatment with heparin and oral anticoagulants appeared to prevent the development of further pulmonary emboli.

Right atrial thromboemboli are rarely diagnosed clinically, but reports of their recognition by cross sectional echocardiography have appeared recently.[1-7] As no series of patients is available it is necessary to build up a picture of the value of the technique from case reports. The information needed is: whether cross sectional echocardiography can differentiate between thrombus and tumour; whether abnormal echoes originate in situ or migrate from peripheral veins; and whether the appearance and character of the echoes can help in deciding optimum treatment. Here we describe a patient who presented with pulmonary embolism and cross sectional echocardiographic evidence suggesting a right atrial thrombus protruding through the tricuspid valve.

Case report

A 78 year old woman was admitted in congestive cardiac failure. She gave a 10 year history of atrial fibrillation, hypertension, and thyrotoxicosis. Auscultation showed a pansystolic murmur at the apex. One week later she developed pleuritic pain with haemoptysis, which was thought to be caused by a pulmonary embolus. Cross sectional echocardiography before the probable embolus had shown a considerable amount of pericardial fluid and mitral annular calcification. A week later the pericardial effusion had resolved, but the right atrium contained a large mobile mass protruding through the tricuspid valve (Fig. 1). This fusiform mass undulated, had a distinct acoustic margin, and was attached to the lateral wall of the right atrium.

A week later the cross sectional appearance of the mass showed that it had reduced in length and was no longer protruding through the tricuspid valve. She was treated with oral anticoagulants after an initial course of heparin, and no clinical or radiographic signs of recurrent embolism developed subsequently. Three months after the initial demonstration of the mass the echocardiogram showed a broad based, ses-

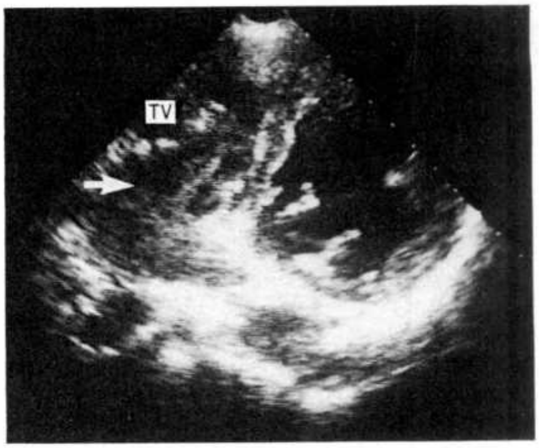

Fig. 1 *Cross sectional echocardiogram in the short axis view at left sternal border showing clot (arrow) attached to right atrial wall and protruding through tricuspid valve (TV).*

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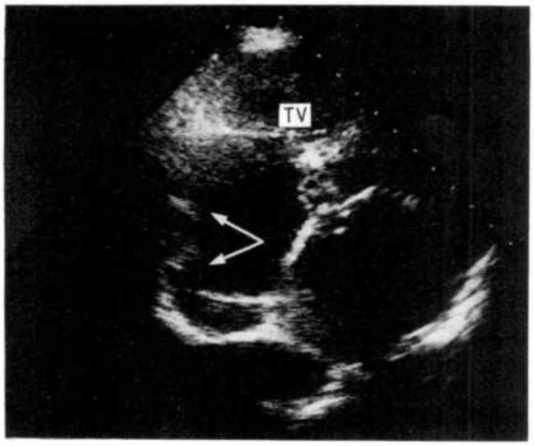

Fig. 2 *Cross sectional echocardiogram in the short axis parasternal view showing sessile clot (arrows) on the lateral wall of the right atrium.*

sile mass on the lateral wall of the atrium at the site of the original attachment (Fig. 2).

Discussion

Using cross sectional echocardiography, right atrial thrombi have been shown to be free floating,[2 3 6] sessile with a broad attachment to the atrial wall,[4] or pedunculated,[5 7] as in the present case. Deduction from individual case reports may be misleading. Thus Redish and Anderson described the mass in their patient as homogenous and regarded the lack of a discrete attachment point as favouring a diagnosis of clot,[6] whereas Manno *et al* stated that the typical appearance of an atrial thrombus was a non-homogeneous, immobile mass with a broad based attachment to the atrial wall.[4]

The main problem in diagnosis is to differentiate between thrombi and tumours. Myxoma is likely if an attachment to the interatrial septum is shown, but right atrial thrombus fixed to the interatrial septum has been described in one patient.[7] Attachment of a pedunculated mass to the lateral wall of the right atrium in our patient and that of Come[5] favoured thrombus or embolus. The nature of the mass in our patient was further suggested by the undulating motion of the elongated echoes and particularly by the reduction in size and the alteration in movement of the mass over the subsequent three months. During that period there was no clinical or radiographic evidence of further pulmonary emboli, which suggests that the echo findings resulted from resolution of the thrombus by retraction against the atrial wall rather than by breaking off of pieces of thrombus. Myxoma could have reduced in size only if myxomatous tissue had broken off to cause pulmonary embolism.

It is impossible to be certain echocardiographically whether the right atrial mass in this case was a thrombus developing in situ or whether it represented an embolus from deep veins. We have referred to the mass as a thrombus because of the absence of any clinical evidence of peripheral venous thrombosis, the low cardiac output state, and the attachment to the atrial wall. Local thrombosis is certain only in patients with foreign bodies such as catheters[8] or a Le Veen shunt[1] in the right atrium.

On detection of a right atrial thrombus or embolus by cross sectional echocardiography the choice is between medical treatment with anticoagulants, streptokinase, or antiplatelet aggregation treatment and surgical management. Patients with these right atrial masses are at risk of sudden death from obstruction of the tricuspid orifice or right ventricular outflow tract and from pulmonary embolism. One patient treated with streptokinase died,[3] as did one receiving aspirin and dipyridamole,[7] and necropsy showed right ventricular outflow tract obstruction by thrombus[6] in a further patient who had died before planned arteriography and surgery.

The use of streptokinase has been questioned: Starkey and de Bono thought that partial dissolution of the thrombus could have led to death from pulmonary emboli in their patient,[3] and Come speculated that streptokinase could deplete plasminogen and promote thrombus growth.[5 9] Operation was ruled out in our patient because of her general frailty, but heparin followed by oral anticoagulants appeared to be successful in permitting resolution of the right atrial thrombus. The general clinical condition of a patient may dictate whether surgery is advisable, and patients such as ours with longstanding, irreversible heart disease are unlikely to obtain prolonged benefit from operation.

Cross sectional echocadiographic investigation should be performed in all patients with pulmonary emboli, as van Kuyk *et al* suggested,[7] but would entail a major increase in workload in many laboratories, and, until the prevalence of cross sectional echocardiographically detectable right sided thrombi in such patients is known, this advice seems premature. At present severely ill patients with pulmonary emboli, and particularly those considered for pulmonary embolectomy, should undergo cross sectional echocardiography.

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Br Heart J 1985; 53: 662–87

Proceedings of the British Cardiac Society

THE 64TH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the University of Birmingham on Wednesday and Thursday, 17 and 18 April 1985. The President, M F OLIVER, took the Chair during private business.

The following were elected to the British Cardiac Society.

New Ordinary Members: F Akhras (London); L D Allan (Kent); S H Armistead (Glamorgan); M Been (Edinburgh); N A Boon (Oxford); H Brown (Newcastle); C Bull (London); J E Burns (Edinburgh); J C Catford (Hampshire); S Chierchia (London); C M Dancy (London); M K Davies (Birmingham); J E Deanfield (London); N G Dewhurst (Edinburgh); S J Edmondson (London); B E Griffiths (Cardiff); D J Gwilt (Buckinghamshire); J D S Higginson (Co Down); J D Hill (Derbyshire); C J Hilton (Newcastle); D W Holt (London); P M Holt (Hertfordshire); E Jackson (Lincoln); M P G Jamieson (Glasgow); O D H Jones (London); H Larkin (Harrogate); P Magee (London); M A Martin (Cheshire); J McComb (Belfast); W J McKenna (London); C A Morley (Leeds); A Murray (Newcastle); J B O'Riordan (London); C Pumphrey (London); I J Reece (Glasgow); R H Robson (Carlisle); F P Shabbo (London); L M Shapiro (London); D F Shore (Southampton); H Singh (Cardiff); R H Smith (Cleveland); A D Timmis (London); B D Vallance (Glasgow); J Weir (Kincardineshire); C Wilson (Co Antrim); N Wilson (Leeds).

New Corresponding Members: A C Arntzenius (Netherlands); P Avogaro (Italy); R Conti (USA); L Ceremuzynski (Poland); T Killip (USA); B Pitt (USA); T W Smith (USA); A Waldenstrom (Sweden); J V Warren (USA).

New Extraordinary Members: D H Makinson, J Norman, G B Shaw, D S Short, R E Steiner.

Resignations: J R Belcher, J M Bishop, J Dark, M B Matthews, A D McInnes, D Verel.

Death: D C Muir.

Elections

D G Julian elected President; J H S Horgan and M Petch elected to Council.

Abstracts of papers

Natural history of patients following intravenous thrombolytic therapy for acute myocardial infarction

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Intravenous thrombolytic therapy (BRL 26921) was administered to 48 patients (31 male, 17 female; mean age 61 years) within six hours from the onset of symptoms. The group was comprised of 23 anterior and 25 inferior infarctions. Reperfusion of the infarct related vessel was confirmed angiographically in 42 (87%) patients, and of these, nine (21%) subsequently reoccluded. Reocclusions occurred between 2 and 11 days postmyocardial infarction and most commonly occurred in patients with severe residual narrowing of the reperfused vessel with poor anterograde flow or in patients where anticoagulant control was suboptimal. There was no correlation between reocclusion and the age or sex of the patient or the time to administration of thrombolytic treatment or the number of diseased vessels present.

All patients underwent follow up for at least six months and up to 12 months. Nine deaths occurred, all within 17 days of myocardial infarction, and these include six patients who showed no evidence of reperfusion or subsequently reoccluded. The other three deaths were among the 33 patients in whom coronary artery reperfusion was demonstrated and vessel patency was maintained. During the follow up period eight (17%) patients subsequently developed angina associated with a positive exercise test, and four of these were treated successfully with surgery. One perioperative death occurred.

Therefore, intravenous thrombolytic therapy with BRL 26921 resulted in a high reperfusion rate, but failure to achieve reperfusion or subsequent reocclusion was associated with an approximately fourfold increase in short term mortality. Residual coronary artery stenoses may result in further ischaemic episodes for which coronary angioplasty or surgery may be indicated.

Reocclusion following coronary reperfusion: incidence, time course and consequences

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A severe residual stenosis is common following acute coronary thrombolysis, and there is concern regarding the further "natural history" of these lesions. In a series of 50 patients with a first myocardial infarction and successful coronary thrombolysis with acylated streptokinase, further episodes of pain occurred in 18. Reocclusion was suggested in nine patients by a second rise in cardiac enzymes and demonstrated at angiography in one without creatine kinase elevation. The standard postreperfusion regimen was heparin for five days followed by warfarin for 3–6 months except when contraindicated. Forty four were maintained on anticoagulation and reocclusion occurred in seven (16%) of these compared with three of six patients in whom anticoagulation was not maintained (50%). Reocclusion occurred at a median time of nine days after initial reperfusion.

Radionuclide ejection fraction was measured routinely at 10 days and again after reocclusion if this occurred later than 10 days. In the group with both measurements the left ventricular ejection fraction fell by 10% (mean) following reocclusion. Intervention coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) was performed in 11 at a median time of eight weeks (range two weeks to 11 months) in patients thought to be at risk of reocclusion causing extensive infarction.

Our results suggest that anticoagulation is important in maintaining reperfusion. Reocclusion occurs most commonly within the first two weeks following reperfusion with acylated streptokinase and may be maintained without major additional interventions. The place of CABG and PTCA following coronary reperfusion requires further study.

Intravenous acyl streptokinase plasminogen complex in acute myocardial infarction

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The use of intravenous streptokinase for patients with suspected acute myocardial infarction has been examined in a district hospital. One hundred and twelve patients with onset of major symptoms within four hours were randomly allocated to receive BRL 26921, an acylated streptokinase-plasminogen complex (55 patients), or conventional treatment alone (57 patients). All had typical symptoms with electrocardiographic changes including ST segment elevation. Fewer patients in the active treatment group than in the control group subsequently showed diagnostic enzyme rises (39 *vs* 50; $p<0{\cdot}05$). The numbers dying in hospital were respectively two and seven. Indices of myocardial necrosis were measured in the two groups. Discharge R wave scores of 51 in the treatment group and 35 in the control group indicated better preservation of myocardial depolarisation after streptokinase ($p<0{\cdot}01$). Release of creatine kinase MB (eight samples over 48 hours) measured as area under the curve was almost identical in the two groups for those who had infarcted, but a trend was noted for peak level to be higher and earlier ($p<0{\cdot}07$) in patients treated with streptokinase. One patient on active treatment had an unusual shower of emboli to the lower trunk and limbs, but otherwise no serious complications were observed.

Acylated streptokinase-plasminogen complex is simple and relatively safe to administer by intravenous bolus and shows promise as a means of reducing myocardial damage after coronary occlusion.

Factors influencing early results of percutaneous transluminal coronary angioplasty

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The results of 306 consecutive coronary angioplasty procedures have been analysed in order to evaluate the factors predictive of angiographic success. Ability to cross the stenosis was the principal determinant of success. Multiple regression analysis of all baseline variables identified six additional factors associated with success. These were the number of dilatations performed, preoperative stenosis, age, male sex, the experience of the operator, and the severity of preoperative angina. Univariate predictors of success by χ^2 testing were the ability to cross the stenosis ($p<0{\cdot}001$) and performing more than five dilatations per stenosis ($p<0{\cdot}05$). Other more weakly predictive variables were preoperative stenosis <90%, age <50 years and male sex ($0{\cdot}05<p<0{\cdot}1$). Of interest were the factors unrelated to success which included elective versus emergency procedures, brachial versus femoral approach, single versus multivessel disease, and single versus multivessel angioplasty. These data illustrate the interaction of both procedural and patient variables in determining the success of coronary angioplasty. Because crossing the stenosis is the principal predictor of success, advances in catheter technology are likely to improve further the early results of the procedure.

Stenosis recurrence following coronary angioplasty: changes in stenosis length

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Stenosis recurrence is the major long term problem following successful percutaneous transluminal coronary angioplasty, and its causes are unknown. Little attention has been given to measurements of stenosis length after recurrence. We have studied the coronary angiograms from 35 of the 41 patients who had a successful outcome from angioplasty when it was undertaken in 50 consecutive subjects. Twenty nine men and six women with a mean age of 50 years were evaluated immediately before and then several months after (5–12, mean 7) successful angioplasty. In every case angioplasty was carried out using balloons with a length of 2·0 cm and a notional diameter of 3·0 mm on inflation. The vessels treated were the left anterior descending artery (29 cases) and the right coronary artery (six cases). Stenosis severity and length were measured directly from tracings of single frames of the coronary angiogram, and the measurements were made (where possible) in three standard radiological projections. Twelve (34%) patients were found to have restenosis; in two of the 12 the treated vessel was totally occluded at the site of dilatation. In the remaining 10 patients with recurrence, the calculated length of the restenosis was greater in seven, similar in one, and less in two patients than the length of the original stenosis. Considering the projection in which the stenosis length was greatest the mean length before angioplasty was 8·8 mm (range 5·8–16·3), whereas several months later the mean restenosis was 10·4 mm (range 8·7–15·3) long, although this did not reach statistical significance.

These results confirm the high frequency of restenosis after successful percutaneous transluminal coronary angioplasty and suggest that coronary angioplasty may induce a longer stenosis.

Absence of late relapse following percutaneous transluminal coronary angioplasty

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Initial analysis of patients who have relapsed following successful percutaneous transluminal coronary angioplasty showed that this had always occurred within the first year. We therefore analysed all relapses occurring in patients who have been followed for more than one year after successful angioplasty. Twenty two of 137 (16%) eligible patients had relapsed after a mean time of 22 (range 1–52) weeks. Six of the 22 (27%) relapses occurred between six and 12 months. The relapse rate in patients followed for more than two years was 9/58 (16%) also. Only one of 11 patients followed for more than three years has relapsed (9%).

Presentation was by recurrence of angina in 75% and by an abnormal exercise test in the remainder. Reangiography was performed in all those who relapsed. No patient was found to have relapsed solely as a result of routine follow up angiography. Early relapse was associated with inadequate dilatation of the original lesion.

In 14% of those relapsing the site of the original angioplasty was still wide open but a new lesion had developed. A further 9% had restenosed at the original site and also developed a new lesion elsewhere. Treatment following relapse was medical in one third, by further angioplasty in another third, and by referral for surgery in the remainder. The longest follow up after reangioplasty was in a patient with recurrence of left anterior descending artery stenosis who is still symptom free on maximal treadmill exercise 3½ years after redilatation.

As one in four of patients who will relapse have not done so at the six months point the calculated relapse rate will be artifically low if patients with short follow ups are included. In this series the relapse rate did not rise during the second or third year of follow up.

Beneficial effect of high dose propranolol treatment in infants with symptomatic hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy presenting with congestive heart failure in infancy carries a grave prognosis, with a mortality of virtually 100%. A high dose (7–10 mg/kg/day) oral propranolol treatment was used in five infants presenting with symptomatic hypertrophic cardiomyopathy confirmed by cardiac catheterisation. The age of presentation ranged from neonatal period to 18 months, and the symptoms included uncontrollable congestive heart failure, failure to thrive, and syncopal episodes. Propranolol treatment caused improvement in all infants; in one infant propranolol treatment was discontinued and he died shortly afterwards from heart failure. The other four are alive and asymptomatic after two to four years follow up. The start of propranolol therapy was associated with disappearance of congestive heart failure, return to normal weight gain, and a gradual improvement in electrocardiographic evidence of hypertrophy with a resolution of abnormal ST and T wave changes. M mode and cross sectional echocardiography has shown regression of abnormal hypertrophy, with in one case virtual return to normal appearances.

It is concluded that propranolol can cause not only symptomatic relief but also partial regression of pathological changes in infants with hypertrophic cardiomyopathy but that a high dose is essential in order to achieve the latter effect.

Spectrum of cardiomyopathies in children: systematic echocardiographic analysis

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Cardiomyopathies are uncommon in children, can prove fatal, and may be associated with generalised disorders. Although the morphological classification applies, there are specific features within some groups which may help to identify secondary myopathies. Between 1975 and 1984, 202 subjects were screened, of whom 91 had the echocardiographic appearance of cardiomyopathy. At presentation 77 were under 10 years old. There were 29 patients with hypertrophic cardiomyopathy, 14 with associated neurological disorders, and one secondary to Pompe's disease. Nine patients had the classical echocardiographic appearance of hypertrophic obstructive cardiomyopathy, two of whom had Noonan's syndrome and two Morquio's syndrome. Only five patients with classical hypertrophic obstructive cardiomyopathy had no underlying disorder and only one had a positive family history.

A total of 59 patients had the echocardiographic appearance of congestive cardiomyopathy, five proved to be related to coronary artery problems, and two had positive viral titres. Only four patients had a positive family history. One case was related to the myeloproliferative form of the hypereosinophilic syndrome. In the remaining 47 there was no obvious aetiological cause. There were three patients with restrictive cardiomyopathy, all idiopathic, and the striking features were the enormous atria with preserved systolic ventricular function.

Cardiomyopathies in children are not uncommonly associated with generalised disorders particularly if they are of the hypertrophic variety. The congestive type is frequently the end stage of an unrecognised insult, but coronary artery problems must be excluded. Unlike the adult group the restrictive form is often idiopathic.

Use of pulsed Doppler echocardiography to assess shunts and gradients in congenital heart disease

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This study compares Doppler measured haemodynamic variables with those found by conventional methods at cardiac catheterisation. The comparison was made in 162 cases. Fifty nine children with obstructive lesions and 41 with pressure gradients across ventricular septal defects were studied using high pulse repetition frequency Doppler. Peak jet velocities were obtained by placing the Doppler sample volume in the jet stream and the pressure gradient calculated using the modified Bernoulli equation ($\Delta P=4V^2$, where V is the peak jet velocity). Right ventricular pressure was predicted by subtracting the ventricular septal defect gradient from the systemic blood pressure.

Flow ratios (QP:QS) were measured by Doppler in 62 patients with intracardiac shunts. Systemic flow (QS) was measured from the suprasternal notch by placing the sample volume in the ascending aorta and obtaining a mean flow velocity ($\bar{V}$). The cross sectional area (CSA) was derived from the aortic diameter; $QS=\bar{V}\times CSA$. Pulmonary flow (QP) was similarly measured from the main pulmonary artery. The Doppler derived QP:QS was compared with that obtained at catheterisation (Fick).

There was good correlation between the two methods for measuring pressure gradients ($r=0{\cdot}94$, $n=100$) and flow ratios ($r=0{\cdot}92$, $n=62$). Predicted right ventricular pressure in patients with ventricular septal defect also correlated well with catheterisation values ($r=0{\cdot}93$, $n=41$).

Percutaneous balloon valvotomy for pulmonary valve stenosis

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Significant pulmonary valve stenosis has usually been managed by surgical valvotomy. We have attempted relief of pulmonary valve stenosis at cardiac catheterisation on 21 occasions in 20 patients between April and December 1984. There were 12 males, eight females (age range 8 days to 12 years, median 31 months, two aged less than 2 weeks). Two patients had Noonan's syndrome, one had an associated right coronary artery to right ventricle fistula, and two had undergone previous surgical valvotomy. The remaining 15 patients had isolated pulmonary valve stenosis. Pulmonary valve annulus diameter was estimated by cross sectional echocardiography to assist in choice of balloon size. Predilatation right ventricular systolic pressures ranged from 41 to 190 (median 92) mm Hg, being suprasystemic on nine occasions. Right ventricle to systemic systolic pressure ratios and pulmonary systolic pressure gradients (mm Hg) were 1·01(0·43) (mean (SD)) and 76·3(41·6) respectively prior to dilatation compared with 0·69(0·29) ($p<0·001$) and 34·3(29·1) ($p<0·001$) immediately following balloon dilatation. Six patients so far have been reinvestigated six months and one patient one week after dilatation. Five had maintained the immediate haemodynamic improvement previously demonstrated. Two patients who had little immediate change in right ventricle to systemic systolic pressure ratio or pulmonary systolic pressure gradient had major reductions in both of these at one week and six months respectively. There were no complications. Percutaneous balloon pulmonary valvotomy appears to provide good short and medium term relief of pulmonary valve stenosis and may obviate the need for surgery in many cases.

Outcome of children with double inlet ventricle presenting in the first year of life

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Definitive repair is now possible for selected older patients with double inlet ventricles. However, the overall outcome of children presenting in infancy with this condition has not been investigated. We therefore studied 107 consecutive patients presenting at less than 1 year of age between 1973 and 1984. Eighty one (76%) had double inlet left ventricle, 18 double inlet right ventricle, and eight double inlet indeterminate ventricle. Sixty two (63%) had two atrioventricular valves and 45 (47%) had a common atrioventricular orifice. Presentation was determined by one or more severe associated lesions (pulmonary stenosis 35, pulmonary atresia 23, aortic coarctation or interruption 25, extracardiac anomalous pulmonary venous connection 15). Fifty one (46%) underwent palliative surgery, but the operative mortality was high (30%): 3/17 systemic-pulmonary shunts, 2/15 pulmonary artery banding, 3/7 atrial septectomies, 8/12 repair of associated lesions. The remaining 56 were initially treated medically either because they had very complex anatomy (29, 25 dead), were unfit for surgery (nine, nine dead), or had balanced physiology (18, four late deaths). Five of the balanced group subsequently required palliative surgery. Among those palliated, five died late (four sudden, one pneumonia), two required a second shunt, and two developed subaortic obstruction after pulmonary artery banding. Of 19/39 survivors for 2 years who were reinvestigated, five were unsuitable for definitive repair (because of subaortic obstruction in two, common atrioventricular orifice regurgitation in one, pulmonary vascular disease in one, distorted pulmonary arteries in one). Only two modified Fontans (one death) and one septation have so far been performed. Thus, even with palliative surgery, only a minority of patients born with double inlet ventricle survive and are suitable for eventual definitive repair.

Patient status 10 or more years after primary total correction of tetralogy of Fallot under the age of 2 years

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Twenty two children who underwent primary total correction of tetralogy of Fallot (irrespective of their anatomy), under the age of 2 years, have been followed up for more than 10 (mean 11·3) years. Their ages at operation were between 3·5 to 24 (mean 13·7) months. Nine (41%) children had additional reconstruction of the right ventricular outflow tract with an aortic homograft monocusp. With a follow up of 10 to 13·25 (mean 11·3) years, there have been no late deaths. The first child in the series required reoperation at 28 months for relief of residual right ventricular outflow tract gradient. (He did not have an outflow tract reconstruction at the first operation.) All children are asymptomatic and have a normal exercise tolerance. Four (44%) children with homograft reconstruction and three (23%) without developed soft pulmonary diastolic murmurs 2–4 years after operation. This murmur has not become louder and the cardiothoracic ratio (mean 0·54) on chest radiograph has not increased with time, neither has the right ventricular/left ventricular dimension obtained from routine M mode echocardiography, at the level of the tip of the mitral valve. Ventricular ectopics have not been noted on either the standard electrocardiogram or 24 hour monitoring. Sixteen children have an axis of 0° to 30°. All patients have been routinely reinvestigated by cardiac catheterisation and angiography two weeks to 12 years (mean 27 months) after operation. In 20 (91%) patients the peak systolic right ventricular to left ventricular ratio was between 0·2 to 0·4 and the right ventricular outflow tract gradient less than 15 mm Hg. There was no increase in ratio or gradient with time in those patients who obtained adequate relief of their right ventricular outflow tract obstruction at operation.

It is concluded that primary total correction of tetralogy of Fallot, under 2 years of age, continues to give good clinical and haemodynamic results more than 10 years after operation.

Treatment of sustained ventricular tachyarrhythmias by electrophysiologically directed drug therapy

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To determine the effectiveness of antiarrhythmic treatment directed by electrophysiological study, 161 consecutive patients with inducible sustained ventricular tachyarrhythmias (136 ventricular tachycardia and 25 ventricular fibrillation) underwent 440 drug studies. The ventricular stimulation protocol included single, double, and triple extrastimuli during sinus rhythm and two paced cycles at two right ventricular sites. Drug success, defined as the induction of ≤ 15 complexes, was obtained in 95 studies, with at least one successful treatment identified for 63 of the patients. Of the 150 patients completing serial drug testing, 53 (group A) were discharged taking treatment identified as successful by electrophysiological study. Ninety six patients (group B) were discharged taking therapy which did not prevent arrhythmia induction; in 81 of these the treatment included amiodarone. Over a mean (SD) follow up period of 16(9) months (range 2 weeks to 35 months) there were nine (17%) sudden deaths/arrhythmia recurrences in group A and 36 (38%) in group B ($p<0·0003$). In group B, there was no difference in recurrence rate between those taking amiodarone and those other treatment ($p=0·54$). In conclusion the chronic effectiveness of medical treatment in patients with sustained ventricular tachyarrhythmias can be determined by electrophysiological study and the validity of this approach is not influenced by the use of amiodarone.

Automatic detection of cardiac arrhythmias by analysis of electrogram morphology

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Pacemaker recognition of pathological tachycardia currently relies on heart rate analysis. Sinus tachycardia on exercise or after arrhythmia termination are thereby commonly mistaken for pathological tachycardia. To overcome this, we have developed a potentially implantable computerised method of automatic arrhythmia recognition. This operates independently of changes in heart rate by analysing the changes that occur in the intraelectrogram sequence of gradients during arrhythmias.

In 12 patients bipolar electrograms were obtained from conventional endocardial pacing sites in the atrium (six patients), ventricle (three), and both (three) during sinus rhythm (three pre-excited) at rest and exercise and during a total of 14 abnormal rhythms: orthodromic atrioventricular re-entry tachycardia (AVRT) with or without left bundle branch block (four), antidromic AVRT (one), atrioventricular nodal tachycardia (AVNRT) in five, and ventricular tachycardia (VT) in four. Patient posture and respiration were varied during all rhythms. The electrograms were recorded at a band pass of 0·16–1 kHz and digitised at a frequency of 2^{11}

Hz before analysis by electrogram gradient pattern detection. Gradient pattern of atrial electrograms during sinus and abnormal rhythms distinguished AVRT and AVNRT from sinus rhythm in all patients. Gradient pattern detection of ventricular electrograms differentiated sinus rhythm from VT in all patients, orthodromic AVRT from pre-excited sinus rhythm in both patients, sinus rhythm from antidromic AVRT in one patient (partial *vs* complete pre-excitation), and intermittent left bundle branch block during AVRT in one patient. Although alterations in amplitudes of atrial electrograms occurred with respiratory and postural variation in four patients, the electrogram morphologies and hence gradient pattern detection were unaffected. It is concluded that gradient pattern detection reliably detects arrhythmias at atrial and ventricular level and overcomes a major problem of present day antitachycardia pacemakers.

Reliability of the QT interval in determining the pacing rate in patients with the TX pacemaker

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The TX pacemaker uses a conventional electrode to sense T waves of paced ventricular complexes, and it adapts the pacing rate to varying physiological demands by responding to changes in the QT, or more correctly stimulus artefact-to-T wave apex interval. This pacing system was assessed in 13 patients. Relation of heart rate to stimulus to T interval and effect of programming on rate changes during exercise were studied on several occasions in each patient. Exercise performance during TX and asynchronous ventricular demand (VVI, 70 beats/min) pacing modes were compared.

T wave sensing was successful in 12 patients. Chronic deterioration in T wave sensing, however, occurred in most patients. The relation of heart rate to stimulus to T interval was found to be described by the following linear regression equation: stimulus to T interval$=590-1{\cdot}58\times$paced heart rate, $r=-0{\cdot}62$. This relation, however, was subject to wide interpatient and intrapatient variation. Consequently, given identical programmed variables and exercise protocol, the quality of rate response varied widely from patient to patient and in the same patient from one occasion to another. Treadmill exercise tolerance, however, was significantly better in the TX mode: total distance (yd) walked on treadmill (mean (1 SD) for TX mode 784(454) and VVI mode 511(352), $p<0{\cdot}01$).

Our results therefore show that, although appropriate and worthwhile rate adaptation can be achieved in most patients, frequent programming, based on results of exercise tests and Holter monitoring, may be necessary to adjust for changes in T wave sensing and relation of heart rate to stimulus to T interval relation and thus ensure that the pacemaker continues to function optimally.

Pace mapping: a valuable alternative technique for localisation of the accessory atrioventricular pathway at surgery

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Localisation of the accessory atrioventricular pathway for surgical ablation may be impossible by activation mapping if anterograde and retrograde conduction via the atrioventricular pathway is temporarily lost during the procedure. The technique of pace mapping was used in five patients undergoing such surgery. A 12 lead electrocardiogram was recorded with a clear delta wave, during sinus rhythm or atrial pacing both before surgery and if possible after exposure of the heart. Pacing pulses were applied to sites around the atrioventricular ring first epicardially and then endocardially until the pattern of the initial deflection of the QRS complex matched that of the previously recorded delta wave in all 12 leads. This site was cut and cauterised. In two patients activation and pace mapping were performed and the sites identified by the two techniques coincided. In the other three patients accessory atrioventricular pathway conduction was lost and successful division was achieved by pace mapping alone.

It is concluded that pace mapping is a valuable additional technique in surgery for Wolff-Parkinson-White syndrome.

A randomised trial of heart valve prostheses

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Between December 1975 and August 1979, 540 patients undergoing valve replacement were entered into a randomised trial and received either a mechanical (Björk-Shiley, 274 patients) prosthesis or a porcine heterograft valve (initially Hancock, 106 patients, and latterly Carpentier-Edwards, 160 patients). Analysis of multiple variables showed the treatment groups to be well randomised. For mitral valve replacement (268 patients) there was an unexplained excess hospital mortality of 16·4% associated with the Carpentier-Edwards valve compared with 7·6% overall. There was no significant difference in hospital mortality for the different prostheses for aortic valve replacement (210 patients), 8·5% overall, nor for the combined valve replacement (62 patients), 14·5% overall.

Mean follow up was 5·6 (range 2·8–8·3) years. The actuarial survival curves for both aortic valve replacement, mitral valve replacement, and the combined valve replacement for the three prostheses remained similar for 7·5 years. Actuarial survival at 3·3, 5, and 7·5 years following mitral valve replacement was 70·6%, 67·2%, and 51·8%: for aortic valve replacement, 83·6%, 80·1%, and 67·7%; for the combined valve replacement 74·7%, 72·9% and 62·5% respectively. Thirty four patients underwent valve rereplacement: 13 Björk-Shiley, 10 Hancock, and 11 Carpentier-Edwards prostheses (p=NS); 12 died at reoperation (operative mortality 35·3%).

There was no significant difference in the incidence of thromboembolism for the different prostheses up to seven years after surgery though approximately 50% of patients with heterograft valves were not anticoagulated. Complications of anticoagulation were rare and occurred in only 16 patients over the course of the study.

It is concluded that up to 7·5 years there is no significant difference in the outcome of valve replacement with the three prostheses studied, but further follow up is necessary as important differences may still emerge.

Recent experience with acute ventricular septal defect: the case for immediate surgery with restricted use of balloon pumping

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From 1980 to 1984, 29 patients with an acquired ventricular septal defect have been treated by a policy of increasingly early surgery after immediate investigations on admission to our hospital. Twenty five patients had defects associated with an anterior myocardial infarction and four with an inferior myocardial infarction. The mean age was 66 (range 48–77) years and the mean time interval from onset of murmur to operation was 10·3 (range 1–60) days, a reflection of delayed referral. Twelve patients were in cardiogenic shock (blood pressure <80 mm Hg, poor peripheral perfusion, and urine <300 ml in 24 hours). Coronary angiography in 28 patients (one arrest, no study) showed one vessel disease in 38%, two in 19%, and three in 38%. Only five patients early in the experience had preoperative balloon pumping. Double patch closure of the ventricular septal defect with infarctectomy in eight patients and saphenous vein grafting in 14 was undertaken. Two patients had cardiac massage to bypass and two required immediate postbypass balloon pumping. Overall hospital mortality at 30 days was 33% reducing to four of 19 (22%) in the last two years. Mortality in the presence of cardiogenic shock was 58% and renal failure (>20 mmol/l) was 40% and infarctectomy 0%. Two recurrent ventricular septal defects occurred, one requiring reoperation. Death resulted from myocardial failure in three patients, multiorgan failure in three, and cerebrovascular disease in one, and there were two sudden deaths five days and three weeks after an initial satisfactory postoperative course. The policy of early closure of ventricular septal defect with resection of large infarctions and simultaneous bypass grafting seems appropriate. Referral to a surgical centre prior to the onset of cardiogenic shock or renal failure should achieve better results. Preoperative intra-aortic balloon pumping has a very limited role in current management.

Left ventricular contractile state and reserve capacity in humans after cardiac transplantation

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Limited data are available concerning left ventricular contractility and contractile reserve in the denervated human heart. The slope value of the relation of left ventricular end systolic pressure to dimension is a load independent sensitive index of contractility which can be determined using echo and calibrated carotid pulse tracings. This index was studied in 10 transplant patients (aged 48(4) years; interval between operation and study 1·2(0·8) years). None of the patients had evidence of rejection by biopsy. Results were compared with data from 10 normal control subjects (aged 25(4) years) matched for donor heart (aged 25(6) years). Baseline left ventricular contractility was assessed over a wide range of afterload generated by methoxamine infusion. Contractile reserve was measured during infusion of methoxamine plus 5 mg/kg/min of dobutamine.

Baseline heart rate and values after drug infusion for controls were 88(21) and 97(20) beats/min respectively ($p<0.01$); the corresponding values for transplant patients were 92(6) and 117(8) beats/min ($p<0.01$). The difference between baseline values for controls and transplant patients was not significant; that between values after drug infusion for the two groups was significant ($p<0.01$). Control baseline values and those after drug infusion for the slope value of the relation of end systolic pressure to dimension were 104(13) and 129(15) respectively; the corresponding figures for transplant patients were 99(9) and 126(12) respectively. The differences between both groups for baseline values and those after drug infusion were not significant.

It is concluded that the transplanted human heart had normal baseline and reserve contractile capacity while demonstrating an augmented chronotropic response. Chronic denervation does not appear to alter left ventricular contractility in humans.

Function of the transplanted heart in long term survivors

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Thirty eight heart transplant recipients were studied in detail after five years (one patient), four years (four patients), three years (six patients), two years (11 patients), and one year (16 patients). Six of these patients subsequently died; two of lung cancer and four of coronary artery disease, of whom two had no angiographically detectable lesions. One patient has been retransplanted for coronary artery disease, and another six have angiographically demonstrated lesions from one to five years after transplantation. Annual study of transplant function included right and left heart catheterisation and right ventricular biopsy. Response of preload and afterload pressures, cardiac output, and pulmonary and systemic vascular resistance to maximal exercise testing was investigated. The grouped data show that (*a*) cardiac function of the transplanted heart provides for normal output response to exercise; (*b*) normal functional responses are maintained without significant decline for one to five years; (*c*) the normal neurally mediated physiological rate response is absent but is compensated by stroke volume response; (*d*) abnormally high preoperative pulmonary vascular resistance returns to normal and shows a wide range of change in response to exercise; (*e*) patients receiving cyclosporin A have an abnormal systemic pressure and resistance response; (*f*) there is no evidence of motor reinnervation of the transplanted heart; and (*g*) good function is maintained in the presence of significant coronary stenoses and occlusions.

Symptoms plus exercise test: a reliable basis for managing angina?

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The practice of basing the diagnosis and management of patients with suspected coronary disease on the history and exercise test alone is generally considered inadequate. The diagnostic and prognostic value of a simple method of patient classification based on symptoms and exercise testing was tested in 300 patients with suspected angina, reviewing their progress after 36–48 months. Patients with typical pain and positive exercise testing (ST depression or elevation) were classified as having coronary artery disease (group 1); those with atypical pain and a negative exercise test (at target heart rate) as not having coronary artery disease (group 2); and those whose type of pain conflicted with their exercise test, or who failed to reach target heart rate, as having possible coronary artery disease (group 3). In group 1 ($n=186$), 122 underwent coronary arteriography, and 121 had significant coronary artery disease (99% specificity). Nineteen coronary deaths occurred. In group 2 ($n=41$), none had arteriography and no coronary events occurred. In group 3 ($n=73$), 22 underwent arteriography; 13 were normal. Two coronary deaths occurred, both in patients with severe angina who were studied angiographically. In group 1 patients, an exercise test duration of six minutes or less appeared to identify a subgroup (n=71) who required urgent surgery (coronary artery bypass grafting): seven of the 26 (27%) who did not undergo grafting died or suffered an ultimately fatal myocardial infarction within four months of their exercise test. This contrasted with a 3% annual mortality among 45 patients in this subgroup who underwent grafting and with a 1·3% annual mortality among 82 non-surgically treated group 1 patients who exercised for longer than six minutes. It is concluded that the combined use of symptoms and exercise testing can be relied on to identify patients in whom arteriography is superfluous and those requiring urgent grafts.

What is the need for coronary artery bypass procedures?

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During the six year period 1979–84, 518 patients were referred by a district general hospital for invasive investigation and cardiopulmonary bypass procedures. The resident catchment population was 202 000. There was a sevenfold increase in the number of patients undergoing coronary artery bypass graft procedures during this period while the requirement for valve surgery showed little growth. The need for grafting plateaued in 1982–4, and based on the figures for 1982–3 (the data for 1984 as yet incomplete) there was a requirement for 330 procedures/million population/year after correction for cross boundary inflow. The requirement for valve surgery during this period was 61 procedures/million population/year. Analysis of the clinical and angiographic data indicates that if grafting had been offered only for angina ($\geqslant$NYHA grade II in patients receiving maximal drug therapy) the requirement would have fallen to 204 procedures/million population/year, although this would have increased to 215 procedures/million population/year if surgery was also offered for significant left main stem disease. Two hundred and eighty one and 305 procedures/million population/year would have been required respectively if patients with significant three vessel and two vessel with significant left anterior descending stenosis were also included. The health district concerned (North West Surrey) has a standardised mortality ratio of 0·78 for cardiovascular diseases, and these figures therefore probably underestimate the need for coronary artery bypass grafting nationally. By extrapolation, however, the national need for surgery for symptoms alone appears to be at least twice the present provision, three or four times the present provision being required if surgery is also offered to improve prognosis.

Non-invasive testing and coronary arteriography in patients with unstable angina pectoris

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In patients with unstable angina the diagnostic accuracy of thallium scintigraphy combined with maximal exercise stress testing related to coronary arteriography is unknown. During 124 consecutive acute admissions with spontaneous chest pain at rest in the absence of acute myocardial infarction, 110 patients had a maximal exercise stress test with thallium scintigraphy. In 66 this was followed by coronary arteriography. Fifty four patients had a positive angiogram (stenoses $\geqslant$ 50%) in the disease distribution: single vessel 15 (28%), double vessel 17 (31%), triple vessel 20 (37%), and main stem two (4%). Of these, 28 had a positive exercise electrocardiogram ($\geqslant$2 mm ST segment depression), two a negative electrocardiogram, and 24 an inconclusive electrocardiogram (no electrocardiographic changes but inadequate heart rate). Fifty of 54 with coronary artery disease had a positive thallium scan (reperfusion, fixed defect or both). When the exercise electrocardiograms and thallium scan were combined and a positive result from either or both obtained then non-invasive testing predicted coronary artery disease in 52 of 54 patients. The two cases missed had single vessel disease. Of the 12 patients without angiographic coronary artery disease, eight were normal and four had other cardiac diagnoses (two mitral valve prolapse, one hypertrophic cardiomyopathy, and one left ventricular hypertrophy). Of the eight normals, one had a negative exercise electrocardiogram, two a positive one, and in five it was inconclusive. Four had positive thallium images and four negative.

It is concluded that maximal exercise testing early after the identification of patients with unstable agina is safe but that the exercise electrocardiogram on its own is poorly predictive and should not be used to exclude ischaemic heart disease (28/54, 52%). Thallium scintigraphy combined with the exercise electrocardiogram greatly improved diagnostic accuracy (52/54, 96%).

Risk stratification following myocardial infarction: a comparison of the Norris index and exercise testing

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Recent controversy surrounds the ability of predischarge exercise test to predict subsequent cardiac events in survivors of acute myocardial infarction. In contrast, the Norris prognostic index remains a recognised descriminant of high risk. To determine the relative value of these potential risk markers the results of predischarge exercise testing and the Norris index were compared with the clinical outcome in 350 survivors of acute myocardial infarction followed for a mean of 12 months. Exercise testing was performed at a mean of nine days and defined as positive by ST segment depression $>0\cdot1$ mV in any of the 12 leads recorded or exertional hypotension or both. On clinical grounds, 50 of the 350 patients were considered unable to perform predischarge exercise. These 50 patients had a higher Norris index (7·0 *vs* 4·43; $p<0\cdot01$), higher mortality (18% *vs* 5%; $p<0\cdot01$), higher frequency of heart failure (52% *vs* 12%; $p<0\cdot01$), and recurrent infarction (20% *vs* 8%; $p<0\cdot05$) than the 300 patients able to exercise. In the 300 exercise patients, however, the Norris index in 170 patients with positive tests (4·38(1·7)) was similar to the index in 130 patients with negative tests (4·49(1·7)). In contrast, mortality (7% *vs* 2%), recurrent infarction (13% *vs* 2%; $p<0\cdot001$), heart failure (22% *vs* 2%; $p<0\cdot001$), angina (58% *vs* 9%; $p<0\cdot001$), and cardiac surgery (22% *vs* 2%; $p<0\cdot001$) were significantly more common in those with positive tests compared to those with negative tests.

These data support the clinical value of the Norris index as a marker of high risk following acute myocardial infarction. In terms of both mortality and morbidity, however, predischarge exercise testing provided a more sensitive risk stratification in infarct survivors.

First dose hypotension with angiotensin converting enzyme inhibitors in heart failure

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In patients with heart failure first dose hypotension with captopril is thought to be uncommon, occurring only in subjects with markedly increased plasma renin; it has been suggested that enalapril does not cause this owing to its delayed onset of action. In a series of 100 such administrations (75 captopril and 25 enalapril) in 68 patients, seven cases of vasomotor syncope occurred (hypotension accompanied by bradycardia and sweating). With enalapril (three cases) the onset of hypotension was later ($>2\cdot5$ h *vs* <90 min), more sustained, and accompanied by evidence of organ damage (myocardial necrosis or renal dysfunction). In those monitored invasively profound falls in pulmonary artery diastolic pressure accompanied or preceded syncope suggesting that a fall in venous return rather than a loss of peripheral arteriolar tone was involved. Large increases in plasma adrenalin but not noradrenalin during syncope suggested a dissociation of adrenal and sympathetic neuronal responses. Two recovered spontaneously, two responded to head down tilt and intravenous atropine, and three required intravenous angiotensin II. Two showed a poor response to this until given intravenous saline.

Neither clinical state, aetiology of heart failure, pretreatment mean blood pressure (60–100 *vs* 56–119 mm Hg), serum sodium (127–141 *vs* 125–150 mmol/l), plasma active renin (41–2234 *vs* 5–6687 uU/ml), nor angiotensin II contentrations (25–284 *vs* 0·5–292 pmol/l) reliably predicted syncope. (Figures are ranges for hypotensive and non-hypotensive groups respectively.) Thus first dose hypotension is difficult to predict. Patients should be observed for some hours after dosing with converting enzyme inhibitors and angiotensin II, and saline infusions should be readily available.

Prolonged clinical benefit of enalapril in treatment of congestive cardiac failure

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Angiotensin converting enzyme inhibition is a valuable form of vasodilator treatment of congestive cardiac failure. Enalapril is a new angiotensin converting enzyme inhibitor with a long (12 hours) duration of action. Fifty five patients with chronic congestive cardiac failure receiving diuretics and digoxin had enalapril (10 mg per day) or placebo added to their treatment and were assessed over six months on a random double blind basis. Mean exercise times on a treadmill to the Naughton protocol at baseline, after one month, and after six months were for placebo 513, 549, and 562 s respectively and for enalapril 596, 683, and 737 s respectively. The difference in values after one month and after six months between placebo and enalapril were significant ($p<0{\cdot}001$). There were no significant changes in ejection fraction, heart rate, blood pressure, weight, and haematological or biochemical values with either enalapril or placebo. Of 27 placebo patients, two died and two were withdrawn with worsening cardiac failure. With 28 enalapril patients one died and three were withdrawn with hypotensive symptoms.

This study, the longest yet of an angiotensin converting enzyme inhibitor for congestive cardiac failure, has shown sustained clinical improvement over six months for patients receiving enalapril.

Ultrafiltration in refractory congestive heart failure

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Nine patients with congestive heart failure refractory to conventional medical therapy with digoxin, diuretics, and vasodilator therapy were treated using ultrafiltration. All patients had severe symptoms (NYHA class IV) and gross peripheral oedema. A mean (SD) fluid loss of 12·6(6·6) (range 3·7–23 l) produced a mean weight reduction of 7·7(5·1) kg immediately following ultrafiltration and 9·9(6·2) kg ($p<0{\cdot}02$), prior to hospital discharge. Improvement was sustained and the patients again became responsive to medical therapy. Electrolytes improved, serum sodium rising from a mean of 128(5) mmol/l to a mean of 132(5) mmol/l ($p<0{\cdot}02$). Haemodynamics were measured in six patients: right atrial pressure fell from a mean of 19(1) mm Hg to a mean of 14(4) mm Hg ($p<0{\cdot}05$), but cardiac output as measured by thermodilution remained unchanged (3·2(0·7) l/min and 3·3(0·5) l/min). Heart rate, blood pressure, and left and right ventricular dimensions measured by M mode echocardiography remained unchanged throughout.

In conclusion ultrafiltration promotes fluid loss and affords sustained symptomatic relief providing a favourable alternative to the treatment of severe congestive heart failure resistant to other forms of medical therapy.

Can the pumping capability of a failing heart improve with inotropic stimulation?

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The beneficial effects of the inotropic agents used in the treatment of severe cardiac failure are often coupled to their vasodilatory effects. When these agents are used in patients with minimal pumping reserve, the vasodilatory effects would predominate. A means of separating the direct effects of the inotropic agents on the cardiac pumping capacity from their vasodilatory effects is required. A new technique was devised to fufil this aim, and it was tested by infusing dobutamine at graded incremental doses to 12 ischaemic cardiac failure patients in NYHA classes III and IV. The haemodynamic data were obtained using a thermodilution Swan-Ganz catheter. At each infusion rate of dobutamine the left ventricular power output (W = cardiac output × mean arterial pressure) was calculated, and the range of power output values resulting from the concomitant change in the peripheral resistance was also determined. A power output value that was found to be above the range defined by the latter signified a direct increase in the cardiac pumping capacity resulting from the inotropic challenge. Five patients (group A) could demonstrate definite augmented pumping capacity to dobutamine challenge; three patients (group B) could increase the left ventricular power output secondary to the vasodilation; and four patients (group C) had maximum power output which did not exceed 1·2 W at any rate of dobutamine infusion. The prognosis of group C patients was grave in that three of them died within one month of the study and the remaining patient required transplantation.

It is concluded that direct effects of dobutamine on cardiac pumping can now be separated from its vasodilatory effects and that the pumping capability of the heart evaluated thereby reflects the amount of viable myocardium present in the left ventricle. Such information would be of therapeutic and prognostic significance.

A radionuclide model of acute myocardial infarction

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To construct a model of the relation of infarct size to left ventricular function in acute myocardial infarction, 65 patients were imaged in the acute phase to acquire thallium 201 tomograms and a technetium-99 m gated blood pool study using a rotating slant hole collimator and mobile gammacamera. Percentage of normal left ventricular function measured by left ventricular ejection fraction, regional wall motion score, and phase analysis was plotted for each patient against percentage volume defect from reconstructed thallium tomograms, previously shown to correlate (r=0·82) with pathological infarct size.

A non-linear relation was seen between deterioration in left ventricular function and thallium defect size, better visualised by regional indices of wall motion score and phase analysis than by global left ventricular ejection fraction. A greater than 40% volume defect in thallium tomograms was associated with accelerated deterioration in left ventricular function. A 45% volume defect showed the widest spectrum of associated left ventricular function. Anterior infarcts were associated with the largest left ventricular perfusion defects and deterioration in left ventricular function, although extensive inferior infacts showed comparable results.

Thus there may be a critical infarct size above which left ventricular function may deteriorate rapidly and approaching which value attempts to limit infarct size may be most important. The variable left ventricular function shown at this critical defect size probably reflects the ability of non-infarcted cardiac muscle to compensate for the infarct.

Myocardial perfusion: an assessment by parametric digital subtraction angiography

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There is a need for the objective assessment of myocardial perfusion, which may supplement the anatomical information obtained by selective coronary arteriography. Digital subtraction angiography with parametric analysis was used to study six patients: Following conventional angiography a timed sequence of images was acquired in arrested respiration, during and after selective left coronary injection of electrocardiogram; three images were stored per cardiac cycle for up to 20 cycles. This allowed subsequent optimisation of the image sequence, minimising movement artefact. The images were all stored as 512 × 512 pixel matrices, offering 0<3 mm of spatial resolution. Subsequent computer analysis defined a time density curve for each pixel. The time of peak arrival of contrast (T-MAX) and the time of ½ peak arrival of contrast (T-½MAX) were colour coded into two parametric images, with normalisation to a heart rate of 70 beats/min. The colour coding permitted easy appreciation of overall myocardial perfusion (T-½MAX) and allowed objective measurement of coronary artery to coronary sinus transit time (T-MAX). Two of the six patients had normal coronary arteries; in these cases the transit time from coronary artery to the myocardium was 7 s and the transit time from the coronary artery to the coronary sinus was 10 s. The remaining four patients had varying degrees of disease severity. The amount of delay in both transit times reflected the amount of left coronary artery disease. Following administration of sublingual vasodilators the abnormal delays were reduced and the transit times fell. In one case with severe left coronary artery disease the artery to sinus and artery to myocardium transit times were 13 and 9 s respectively. These times fell to 11 and 8 s respectively following vasodilatation.

This method may permit objective assessment of myocardial perfusion and supplement anatomical information.

Clinical measurement of ventricular dimensions and stroke volume using magnetic resonance

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Magnetic resonance provides a unique non-invasive means of delineating cardiac function and structure. Measurements taken from magnetic resonance sagittal, coronal, and transverse sections were compared with corresponding measurements from anteroposterior and lateral angiograms in 20 male patients. A GEC/Picker superconductor machine at 0·24 Tesla with an electrocardiogram R-wave gate was used and magnetic resonance end systolic image data were acquired between 36 and 12 ms prior to A_2. Diastolic image data was taken 34 and 10 ms before the minimum RR interval. A coronal section was taken at the level of the centre of the aortic valve, a sagittal section at the greatest vertical diameter of the left ventricle and a transverse section at the greatest horizontal diameter of the left ventricle. Four angiographic measurements corresponding to the magnetic resonance slices were made as follows: (*a*) vertical diameter in anteroposterior projection, (*b*) vertical diameter from centre of aortic valve to inferior wall on lateral projection, (*c*) transverse diameter on anteroposterior projection, and (*d*) anteroposterior diameter on lateral projection. Significant correlations were obtained from both measurements taken from the anteroposterior angiographic projection ($r=0·50–0·78$) but no significant correlation was found from those obtained in the lateral views. The ability of the magnetic resonance to measure ventricular volumes accurately was further tested in 14 normal subjects by comparing the left and right ventricular stroke volumes using a multislice technique. The right ventricular stroke volume was 74(6) ml (mean (SEM)) and left ventricular stroke volume 72(4) ml ($p>0·05$).

These findings indicate that magnetic resonance provides a non-invasive means of measuring ventricular dimensions and stroke volumes.

Non-invasive assessment of right ventricular function at rest and on exercise in obstructive airways disease

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Non-invasive assessment of right ventricular function is of clinical interest in the patient with obstructive airways disease. Gated xenon-133 scanning allows right ventricular function to be evaluated in isolation from the left ventricle, and with rapid clearance from the lungs scans may be repeated within 5 minutes. Four hundred millibecquerels of xenon-133 were injected intravenously over 20 s and images were obtained gated to the electrocardiogram, using a mobile gammacamera in the 10° left anterior oblique projection with 6° caudal tilt for optimal separation of atrium from lung. Acquisition was initiated when xenon activity reached the right ventricle and was terminated as activity left the ventricle. Maximal symptom limited exercise was performed on a supine bicycle ergometer. The normal range for right ventricular ejection fraction was obtained from 10 volunteers (40–55% at rest rising by 5–15% during exercise). In 10 patients with acute obstructive airways disease, all had reduced values (21(3)%. In chronic obstructive airways disease, if resting values were greater than 30%, ejection fraction increased on exercise. If resting ejection fraction was abnormal then values were reduced or unchanged on exercise (mean 15(9)%), and this was associated with dilatation of both the right ventricle and atrium. In 20 patients in whom simultaneous haemodynamic measurements were made, increased calculated pulmonary vascular resistance at rest tended to be associated with reduced right ventricular ejection fraction. On exercise, however, there was no definite correlation between the haemodynamic variables and the exercise right ventricular ejection fraction response.

In conclusion, gated xenon-133 offers a simple method of assessing right ventricular function at rest and on exercise in patients with obstructive airways disease.

Survival from ventricular fibrillation

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Many factors are involved in predicting survival following ventricular fibrillation. This study identified the most significant factors present at the initial and last arrests which predicted survival to leave hospital. During 1983 125 patients (79 male, 46 female aged 16–91 (mean 64) years) were managed with 173 episodes of ventricular fibrillation: 106 had a single episode, forty six had ventricular fibrillation outside hospital, and 53 survived to leave hospital. At the initial arrest, 86 patients had primary ventricular fibrillation (absence of heart failure or cardiogenic shock). Using single factor analysis of the initial arrest, the place of arrest, aetiology of ventricular fibrillation, coarse ventricular fibrillation—that is, $\geqslant 0·5$ mV before the first shock—or prior treatment with beta blocking drugs, diuretics, or digoxin were not related to survival to leave hospital. Nevertheless, those who had ventricular fibrillation <24 hours from the onset of symptoms ($p<0·02$), received the first DC shock <1 min after ventricular fibrillation developed ($p<0·01$), or who required $\leqslant 5$ shocks to terminate the ventricular fibrillation ($p<0·01$) had a significantly improved long term survival. The average number of shocks required at the first arrest in those who survived to leave hospital was three and for those who did not survive, five. After correction of ventricular fibrillation, if the rhythm was idioventricular, complete heart block, or asystole this was associated with a worse prognosis ($p<0·01$). A discriminant function analysis of the initial arrest showed that if $\leqslant 5$ shocks were necessary to correct ventricular fibrillation the time from onset of ventricular fibrillation to the first shock (<1 min), type of ventricular fibrillation (primary), and absence of antiarrhythmic therapy were of greatest significance in predicting survival. At the last arrest factors of most significance were ≤5 shocks to correct ventricular fibrillation, primary ventricular fibrillation, absence of antiarrhythmic therapy, and absence of a previous cardiac arrest. For the initial arrest the sensitivity and specificity of predicted survival were 59% and 89% and for the last arrest 78% and 75% respectively.

Prognostic significance of ventricular arrhythmia after repair of tetralogy of Fallot: a prospective study

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Ventricular arrhythmia is common after repair of tetralogy of Fallot, but the prognostic significance and the indications for therapy are unknown. A prospective study of 86 patients (59 male, 27 female) who had undergone repair between 1959 and 1978 (at age 3–45 (mean 13·6) years) was performed. All underwent 48 hour electrocardiographic monitoring 4–22 (mean 14·6) years after surgery: 77 (89%) had postoperative haemodynamic data and 38 (44%) radionuclide angiography. Thirty nine (45%) patients had significant ventricular arrhythmia consisting of frequent (>30/hour) uniform extrasystoles (two patients), complex extrasystoles (30 patients), or ventricular tachycardia (seven patients). Only 15 patients were symptomatic (11 palpitation, four syncope). Of these, eight had ventricular arrhythmia, four supraventricular tachycardia, and 10 were started on antiarrhythmic medication. There were no significant clinical or haemodynamic differences between asymptomatic and symptomatic patients. All 86 patients were then followed for a further 44–78 (mean 63) months with no drug treatment given to asymptomatic patients. During this time one patient died suddenly (eight extrasystoles on previous 48 hour monitoring) and only one showed increased symptoms requiring treatment. All high risk patients with complex ventricular arrhythmia or ventricular tachycardia and either high (>60 mm Hg) right ventricular pressures (seven patients) or reduced right ventricular ejection fraction (six patients) remained alive and well. Thus ventricular arrhythmia did not affect the excellent outlook of patients after repair of tetralogy of Fallot, regardless of residual haemodynamic disturbances or impaired ventricular function. There does not appear to be any advantage in potentially dangerous long term prophylactic antiarrhythmic therapy for asymptomatic postoperative patients.

Ablation of atrioventricular nodal conduction using 50 J and an active fixation electrode

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Endocardial ablation of the His bundle has been attempted using high energies and standard pacing electrodes. In this study a reduction in energy requirements was attempted using an active fixation electrode.

Ten patients (five men, five women) aged 34–69 years were studied. Six had paroxysmal atrial fibrillation, three tachycardias due to dual atrioventricular nodal pathways, and one a concealed left accessory atrioventricular pathway. A temporary pacing electrode was inserted into the right ventricle, and a Vitraton Helifix electrode positioned via the right femoral vein to obtain the maximal His bundle deflection. Four shocks of 50 J each were delivered via the latter electrode at one minute intervals. The anodal output of the defibrillator was connected to a paddle placed on the posterior chest wall. Blood for cardiac enzyme estimation was obtained. All patients developed complete heart block immediately post-ablation. This persisted in seven patients, while two had first degree atrioventricular block and right bundle branch block (follow up 2–5 months). These nine patients were all asymptomatic on no drug therapy; eight required permanent pacemakers. Atrioventricular conduction returned in only one of 10. There were no complications. The A:H ratio and creatine phosphokinase values were unrelated to the outcome.

Catheter ablation of normal and abnormal atrioventricular pathways: long term follow up

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In a single centre, 28 patients have been followed for 2 to 37 (mean 16) months after catheter ablation of either normal or abnormal atrioventricular conduction pathways. One had persistent sinus tachycardia, three chronic atrial tachycardia, four paroxysmal atrial flutter, 11 atrial fibrillation, and nine paroxysmal junctional tachycardias. The pathways treated were the normal atrioventricular node His bundle in 20 patients, dual atrioventricular nodal pathways in one, and atrioventricular accessory pathways in six (posteroseptal, 4; anteroseptal, one; left freewall, one), and both a posteroseptal accessory pathway and the atrioventricular node in one. In the patients in whom atrioventricular nodal ablation was attempted, between 1 and eight (mean 3·5) shocks (320 to 350 J) were given. Seventeen (80%) patients have persistent complete heart block, two (10%) have much slower atrioventricular conduction, and two (10%) have had unsuccessful procedures. All but the latter two have received pacemakers and are asymptomatic. In those in whom accessory pathway ablation was attempted from the coronary sinus, between five to 46 shocks of up to 125 J per pole were given. In two there was complete ablation, in two significant modification of conduction, and in two no effect. In the patient with dual atrioventricular nodal pathways five shocks were used, and in the patient with an anteroseptal accessory pathway one shock was used, and both were cured.

All patients are alive. Cardiac enzymes were raised in 23 of the patients (mean serum asparate aminotransferase 99 IU/l (normal <40); mean hydroxybutyrate dehydrogenase 183 IU/l (normal <125)) but no patient suffered clinical infarction or had signs of cardiac decompensation. Complications consisted of early ventricular tachycardia in three, pneumonia in one, and deep vein thrombosis in one. Long term results from atrioventricular catheter ablation are excellent, and the procedure is relatively safe with minimal complications.

Responsiveness of pulsed Doppler cardiac output measurements to changes in left ventricular function

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Clinical validation of non-invasive measures of cardiac output requires not only that they should correlate closely with measures obtained by established techniques but also that they should be rapidly responsive to changing left ventricular function. In the present study simultaneous bedside measurements of cardiac output by thermodilution and by the pulsed Doppler technique were made in 10 patients during incremental atrial pacing, inotropic stimulation (dobutamine 250 to 1000 μg/min IV) and vasodilatation (nitroglycerin 10 to 90 μg/min IV). Fixed rate atrial pacing controlled for changes in heart rate during the drug interventions. A total of 110 cardiac output measurements (ranging from 2·1 to 15·0 l/min) made by both techniques showed a close linear correlation ($r=0{\cdot}90$) described by the regression equation $Y=0{\cdot}15+1{\cdot}04X$ ($p<0{\cdot}001$). Thermodilution cardiac output was not significantly affected by atrial pacing but increased during dobutamine infusion from 5·8(3·2) to 6·9(2·8) l/min ($p<0{\cdot}05$). Nitroglycerin on the other hand lowered thermodilution cardiac output from 6·7(1·9) to 5·6(1·7) l/min ($p<0{\cdot}05$) owing to a reduction in pulmonary capillary wedge pressure from 21·1(4·8) to 12·9(4·4) mm Hg ($p<0{\cdot}05$). Directional changes in Doppler cardiac output measurements in response to the interventions were identical and mean values were always within 0·6 l/min of thermodilution values. The inotropic response to dobutamine was reflected in a sharp rise in peak aortic blood velocity from 70(29) to 89(31) cm/s, but this variable was unaffected by nitroglycerin.

Thus the pulsed Doppler technique provides a reliable non-invasive means of measuring cardiac ouput at the bedside. Importantly, measurements obtained by this technique are rapidly sensitive to changes in output induced by inotropic stimulation or preload reduction.

Cross sectional and pulsed Doppler echocardiographic study of aortic root in idiopathic infantile hypercalcaemia (Williams-Beuren syndrome)

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Idiopathic hypercalcaemia is often associated with supravalve aortic stenosis. In the present study the aortic root anatomy was studied by cross sectional and pulsed Doppler echocardiography. Forty nine successive patients with idiopathic hypercalcaemia (mean age 10·0 years) were studied without regard to the previous documentation of cardiac murmurs or defects. Aortic root was studied by cross sectional echocardiography in the parasternal long axis view and pulsed Doppler echocardiography was used to detect disturbances in the normal flow pattern. The results were compared with normal age matched controls with a mean age of 9·8 years in whom the same procedures were carried out. The internal diameter of the aortic root and ascending aorta were measured in end diastole at (*a*) aortic annulus (D1), (*b*) sinuses of Valsalva (D2), (*c*) sinotubular junction—junction of the aortic root with the ascending aorta—(D3), and (*d*) distal ascending aorta (D4). In the control group the diameter at D3 was greater than D1 ($p<0·005$) whereas in all the study patients D3 was less than D1 ($p<0·001$). Three categories of aortic root abnormality were recognised. (*a*) hourglass constriction at D3 (42/49), (*b*) tubular hypoplasia involving D3 and D4 (5/49), and (*c*) membranous supravalvar diaphragm at D3 (2/49). Pulsed Doppler echocardiography showed dispersion of laminar flow in 42/49 patients and in none of the controls. Such flow patterns were maximal in those with sinotubular narrowing (D3) and with tubular hypoplasia (D3 and D4). Correlation with clinical findings demonstrated that those with absent murmurs had the least sinotubular narrowing and normal Doppler flow pattern.

It is concluded that abnormal sinotubular junction is an inherent feature of idiopathic hypercalcaemia and that its demonstration by cross sectional echocardiography is of diagnostic value. Additionally, serial cross sectional echocardiography and pulsed Doppler echocardiography examinations may be useful in determining the progress and management.

Intravenous adenosine in the treatment of supraventricular tachycardia

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Intravenous adenosine is an effective treatment for atrioventricular re-entrant tachycardia induced in the electrophysiology laboratory. Initial experience using intravenous adenosine in the acute treatment of spontaneous narrow complex, regular tachycardia is presented. Ten episodes of tachycardia were treated in six patients (four male) aged 22–73 years. Adenosine was given in a series of bolus doses, starting at 40 μg/kg, increasing in steps of 40 μg/kg, to the maximum of 200 μg/kg, if required, except for one patient who received an initial dose of 10 μg/kg. Adenosine restored sinus rhythm in seven episodes in three patients, about 10–30 s after the effective dose was injected. Those patients who did not revert to sinus rhythm were shown to have atrial flutter. Two patients were also receiving dipyridamole therapy. In one of these, 40 μg/kg adenosine produced asystole lasting 15 s. In the second patient a dose of 10 μg/kg restored sinus rhythm. This dose contrasts with an effective dose of 120–200 μg/kg in the other patients. Dipyridamole potentiates the effects of adenosine by limiting red cell uptake and degradation. Side effects were usually transient consisting of dyspnoea and facial flushing. Our results suggest that in the treatment of supraventricular tachycardia (*a*) adenosine may restore sinus rhythm in some patients with supraventricular tachycardia, although not in patients with atrial flutter; (*b*) dipyridamole potentiates the cardiac effects of adenosine (dose reduction is advisable if alarming bradycardias are to be avoided); and (*c*) side effects are slight if an appropriate dose of adenosine is given.

Further studies are required to establish efficacy and safety in larger patient groups and to compare adenosine with standard treatment.

Defibrillator waveform and cardiac injury

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Are there differences in the efficacy and safety of different defibrillator waveforms? To study this greyhounds (27·2(0·7) kg) were anaesthetised with pentobarbitone (30 mg/kg IV) and randomised to receive either no shocks (control group), or to one of five groups receiving five synchronised transthoracic shocks at intervals of 30 s: group 1, Lown waveform (underdamped sine wave); group 2, Edmark waveform (critically damped sine wave); group 3, Belfast waveform (overdamped sine wave); group 4, trapezoid (5 ms duration); group 5, trapezoid (20 ms duration). Groups 1 to 3 received 400 J stored energy: in groups four and five, 1100 V were stored on the capacitor. Average first shock delivered energies and peak currents were respectively 286, 277, 267, 130, and 418 J and 55, 68, 58, 27, and 28 A. Three days following the shocks the hearts of six survivors in each group were excised and the weight of damaged tissue was determined after incubation in 1% triphenyltetrazolium chloride. ST segment elevation at one hour after the shocks was significantly greater ($p<0·05$) in group 1 (9·1(SEM 1·7) mV), group 2 (11·7(2·4) mV), and group 3 (14·5(2·2) mV) than in either the control (1·1(0·2) mV) or group 4 (1·8(0·4) mV). Ventricular ectopic activity at 24 hours was significantly greater ($p<0·02$) in group 2 (202(12) per min) and group 3

(216(8) per min) than in any of the other groups (group 1, 113(31): group 4, 23(14): group 5, 118(37). Group 4 did not differ significantly from the control (0·5(0·2) per min). Cardiac damage in the control group (nil) and groups 1 (3·5(1·3) g)and 4(0·7(0·3 g) did not differ significantly. Groups 2 (16·0(3·7) and 3 (21·1(2·9)) showed significantly more damage than any of the other groups ($p<0.05$).

These results suggest that sine wave defibillators vary in their ability to cause damage and that the use of trapezoidal waveforms merits further evaluation.

Incidence and morphology of ischaemic ventricular tachycardia

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Ventricular arrhythmias are a frequent cause of sudden death in patients with coronary artery disease. The incidence and relation of ventricular tachycardia to periods of ischaemia in these patients have not been fully investigated. Forty eight hour ambulatory ST segment monitoring was performed in 74 consecutive patients with coronary artery disease and the recordings for ventricular tachycardia ($\geqslant 3$ beats, rate >100/min) analysed. One patient with single vessel disease (4·5%), one with two vessel disease (4·5%), and four with three vessel disease (13%) had episodes of non-sustained ventricular tachycardia. Four of these patients had ambulatory ST segment changes, but ventricular tachycardia was related to these episodes in only two patients. These patients had multiple (118 and 48) episodes of tachycardia which occurred after the onset of ST segment change and terminated before the ST segment returned to baseline. They occurred in clusters (12(8) episodes in each), which were all associated with ST segment change. ST segment changes did not follow episodes of ventricular tachycardia in any patient. The number of ventricular complexes in each episode varied between 3 and 22 beats and were uniform in four of the six patients. The mean heart rate before the onset of tachycardia was 77(8) beats/min and the rate of tachycardia was 153(29) beats/min. Three of the 21 episodes of tachycardia occurred during the night. Less than 10% of the episodes of tachycardia were initiated with the R on T phenomenon. Although ventricular tachycardia is infrequently associated with periods of ischaemia, when this does occur the episodes are multiple and frequent.

Autonomic tone modulation of atrioventricular accessory pathway conduction

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During sinus rhythm and fixed rate atrial pacing sustained deep inspiration provoked pre-excited QRS complexes in two patients with type B Wolff-Parkinson-White syndrome (aged 26 and 54 years). The anterograde refractory periods of the accessory pathways could not be determined during normal breathing but were 540 and 280 ms lying and 300 and 280 ms standing respectively during sustained deep inspiration. Isoprenaline (3 μg/min) but not atropine (0·04 mg/kg) provoked pre-excitation in sinus rhythm during normal breathing. Atropine as well as propranolol (0·2 mg/kg) decreased the provocation of pre-excitation by sustained deep inspiration. Pre-excitation was provoked only during the first three minutes of exercise but reappeared immediatly after exercise. The vacuum neck collar (pure parasympathetic effect) prolonged the RR interval but did not provoke pre-excitation. The Valsalva manoeuvre at 35 mm Hg for 15 s during sinus rhythm provoked pre-excitation during phase 4 (parasympathetic predominant) in the two patients but not during phase 2 (sympathetic predominant). The effect of the Valsalva manoeuvre was studied in 17 other patients with Wolff-Parkinson-White syndrome. In nine (53%) patients the pre-excitation decreased or disappeared in phase 2 but increased in the early stages of phase 4 in 12 (71%). These effects were not due to changes in the atrioventricular conduction time (AH interval). These observations suggested that pre-excitation was usually provoked when parasympathetic stimulation occurred against a background of high sympathetic tone (as in sustained deep inspiration, Valsalva manoeuvre, isoprenaline infusion, and postexercise). This demonstrates (*a*) the mutual agonistic effect between the sympathetic and parasympathetic tone and (*b*) the importance of sympathetic-parasympathetic balance on the regulation of accessory pathway conduction.

Polyuria associated with supraventricular tachycardias

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Supraventricular tachycardias may be associated with distressing polyuria. The mechanisms of this phenomenon were investigated in six patients in whom tachycardia was initiated by programmed stimulation. Four patients had atrioventricular re-entrant tachycardia and two atrioventricular nodal re-entrant tachycardia. Their ages ranged from 23–72 (mean 46) years. Two patients complained of polyuria. Changes in blood pressure, urinary sodium and free water excretion, and plasma antidiuretic hormone, noradrenaline, and dopamine were assessed during sinus rhythm and tachycardia, urine was obtained by voluntary micturition at frequent intervals, and each patient was water loaded to achieve a constant baseline urine flow. When this was achieved the arrhythmia was initiated by either rapid atrial pacing or atrial extrastimuli and this was performed at a similar time of day in each patient. The mean tachycardia rate during the study was 184 beats/min and the mean tachycardia duration was 28 minutes. Immediately following the arrhythmia there was an increase in free water excretion from a mean of 3·8 ml/min to a mean of 7·8 ml/min in five cases. Sodium excretion increased from a mean of 1·2 mmol/ml to a mean of 1·7 mmol/ml. in four cases and was unchanged in two. In these two cases the arrhythmia was atrioventricular re-entrant tachycardia. There was no correlation between sodium excretion and mean blood pressure during tachycardia. There was no relation between dopamine and noradrenaline concentrations and sodium and free water excretion. Plasma antidiuretic hormone concentrations were consistently low during the study confirming the efficacy of the water loading.

In conclusion this study demonstrates that the diuresis accompanying supraventricular tachycardias is in some cases due to an increase in both free water and sodium excretion but may also be due to an increase in free water excretion alone.

Analysis of pacing policy and outcome in a single district pacing service with high implant rate: over enthusiasm or responsible practice?

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Audit of indications for permanent pacemaker implantation for a single district pacing service was occasioned by discovery of a pacing rate well above the estimated national average (197·9 *vs* 114·5 implants/million population/year for 1981). Over a 5·8 year period 177 patients (97 male and 80 female, mean age 68·9 (range 30–97) years) underwent first implantation of a permanent pacemaker (mean implant rate 179·5/million population/year). Indications for implantation were classified according to guidelines set out by the Joint American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures, published in August 1984. In 144 (81·4%) patients sinoatrial (62·5%) or atrioventricular conduction abnormalities were documented; 104 (72·2%) of these were class I indications (generally agreed indications) and the remainder class II (frequently accepted indications). In 11 (6·2%) patients, although a slow pulse was found during acute episodes, electrocardiographic documentation was never achieved. All but one of these patients were rendered symptom free by pacing. In 22 (12·4%) patients neither a slow pulse nor electrocardiographic documentation was recorded, and pacemaker implantation was prompted by a history thought to be typical of Stokes-Adams attacks. On follow up over periods ranging from 6–42 months, 12 (54·5%) of these were rendered symptom free; eight (36·4%) had symptomatic episodes that seemed different from the ones that had prompted pacemaker implantation and two (9·1%) had no change in symptoms.

It is concluded that this policy of pacing symptomatic patients with sinoatrial abnormalities and carefully selected patients with a history strongly suggestive of Stokes-Adams attacks is an effective approach and results in an acceptably low risk of inappropriate pacemaker implantation.

Initial clinical experience with a new software based tachycardia reversion pacemaker

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Current generation antitachycardia pacemakers suffer from limitations concerning detection and distinction of pathological tachycardia and also from the termination modes available. To overcome many of these limitations, a new device (Intermedics Intertach 262–12) has been developed and has now been tested as an external unit in eight patients and implanted in three. It is small (49 g) and is bipolar with an inline connector. Tachycardia recognition may be achieved manually or automatically using high rate, sudden onset, rate stability, or sustained high rate, alone or in combination. Termination may be effected using 1–250 stimuli, which may be fixed rate or rate related. Extrastimuli or bursts may be scanned with the S_1 and S_2 to Sn intervals being independently programmed. Scanning may start from either preset or from rate related coupling intervals, and there is also a programmable memory function, optionally dependent on interval similarity. Autodecremental bursts (±rate related) are also available. The number and size of scanning (or autodecremental) steps can be programmed, as can the minimum cycle length. Two termination modes, 1° and 2°, may be selected. There is telemetry with full diagnostic functions, and non-invasive electrophysiological studies can be performed. The pacemaker was implanted in three patients, all with atrioventricular nodal re-entrant tachycardia (cycle lengths 260, 300, and 330 ms). They had frequent tachycardias (one, two, and 12 per month) and had all failed drug therapy. Right atrial pacing was used, with seven stimuli in rate related scanning modes. All three devices terminate tachycardias almost immediately without additional drug therapy, and sinus tachycardias have not triggered pacing. This pacemaker represents a considerable advance over previous devices and offers improvements in patient management because of its flexibility.

Ventricular tachycardia masquerading as supraventricular tachycardia: management of His bundle tachycardia

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Until recently, the natural history of children surviving with narrow QRS (His bundle) ventricular tachycardia was unknown. Most reports indicated a poor prognosis and did not provide guidelines for effective treatment. Five children (three girls, two boys aged 5 weeks to 18 months) have presented with His bundle tachycardia at rates of 250–290 beats/min since 1978. Since this ventricular tachycardia resembles supraventricular tachycardia, four had been treated inappropriately with digoxin or verapamil, causing ventricular tachycardia in three and acceleration of His bundle tachycardia in one. Careful analysis revealed ventriculoatrial dissociation on the electrocardiogram in four during His bundle tachycardia. His bundle tachycardia occurred following a viral myocarditis in one; no child had congenital heart disease. Until the age of 3 years, 24 hour electrocardiographic recording was performed three monthly then annually in older children. His bundle tachycardia was suppressed and sinus rhythm in four of the five children (follow up 1·3–6·3 (mean 3·1) years) by disopyramide alone in two, disopyramide and mexilitine in one, and by mexilitine and amiodarone in the other. Disopyramide and mexilitine were used together to control the His bundle tachycardia rate at 100–130 beats/min in the fifth child; attempts to further suppress the His bundle tachycardia resulted in sinus node depression and cardiotoxicity. All treatment has been withdrawn in one child who has been free of His bundle tachycardia for three years. There has been no recurrence thus far three months off all drugs. There has been no apparent adverse effects of long term high dose antiarrhythmic therapy on their physical or academic development. Although intravenous verapamil is usually the most appropriate antiarrhythmic agent for the emergency treatment of narrow QRS tachycardia, the response to this nodal drug must be monitored carefully. If no slowing occurs after two thirds of the recommended dose or if ventriculoatrial dissociation is seen on the electrocardiogram, then His bundle tachycardia should be suspected and treatment replaced with a class I drug—for example, disopyramide.

Prevention of leg wound complications associated with saphenous vein harvesting for bypass grafting using the Mayo vein stripper

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Conventional techniques of vein harvesting are time consuming and may result in serious complications. In an attempt to expedite vein removal without compromising its integrity and prevent the early and late morbidity of open dissection, a prospective study was undertaken to evaluate a method of limited subcutaneous dissection using the Mayo vein stripper. The early and late clinical findings in 297 unselected consecutive patients are discussed. An appraisal of the operative technique illustrating its distinct advantages is presented. The harvesting technique is quick and easy to learn. Limited tissue dissection, reduction in harvesting time, and rapid wound closure expedite the entire surgical procedure. There was no instance of wound dehiscence or frank sepsis and no patient required re-exploration. Superficial wound inflammation occurred in 3% of patients, wound haematoma (mainly groin) in 1·6%, saphenous nerve damage in 1·3%, and persistent leg oedema in 0·3% of cases. Light and scanning electron microscope studies confirm lack of trauma to the main trunk, particularly the tributaries. Symptomatically the patients were notably more comfortable, as manifested by early and improved mobility and a dramatic reduction of early and late morbidity associated with leg incisions, particularly if the patient is overweight, diabetic, or suffered concomitant peripheral vascular ischaemia and neuropathy.

Intraoperative real time scanning during coronary and peripheral vascular surgery: morphological appearances and postanastomotic imaging

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The use of high resolution real time ultrasound was explored intraoperatively during coronary, carotid, and peripheral vascular reconstruction. A 12 MHz scanning probe was used and the findings in 30 patients undergoing myocardial revascularisation and 20 undergoing carotid and peripheral vascular reconstruction were analysed. Scanning was rapidly achieved without any complications. Scanning techniques are described with special reference to the value of postanastomotic and postendarterectomy imaging. The percentage decrease in diameter of 30 coronary angiographic lesions was correlated with the same measurement on the corresponding ultrasonic images. The mean difference was 2·5% (SD 9·8%) and a correlation coefficient of 0·87.

Real time operative ultrasound offers a safe, rapid, and readily available means of obtaining high resolution images in multidimensional views with sufficient detail to allow accurate estimates of luminal diameter and quantitative assessment of obstructive lesions. It is useful in identifying obscure coronary arteries and selecting suitable anastomotic sites thereby aiding decision making. Postanastomotic imaging defines technical errors, allows early correction of defects when indicated, and provides feedback on surgical techniques.

Valve surgery for active infective endocarditis: factors affecting mortality

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A retrospective study was conducted into the causes of mortality in patients undergoing valve surgery during active infective endocarditis (1975–84). All 48 patients included in the review continued to show signs of active infection at the time of operation. Resistant heart failure and inadequate response to antimicrobial treatments were major indications for surgery. Eighty five percent (n=41) had positive blood or valve cultures; 61% of these had streptococcal and 34% staphylococcal infections. Perioperative mortality (surgery 30 days) was 27% (n=13), most fatalities being during induction of anaesthesia or at surgery. There was a 75% mortality of *Staphylococcus albus* prosthetic endocarditis. The overall mortality of streptococcal and staphylococcal infections of native valve endocarditis was similar (15%). Only one patient died, however, out of 12 with *Streptococcus viridans* endocarditis. As expected patients with impaired renal function (judged by preoperative blood urea and creatinine) had a higher mortality. There was no difference in duration of antibiotic treatment prior to surgery between the fatal and nonfatal groups. Seven out of 35 developed postoperative paravalvar leaks, five requiring reoperation. Two developed fatal aneurysms of ascending aorta 18 to 28 months postoperatively at the site of the aortic vent.

The overall mortality reported in medically treated endocarditis is in the region of 25% with 60% mortality in patients with heart failure. Apart from the present cases with *Staph albus* infections of prosthetic valves that had a high mortality the perioperative mortality in these relatively sick patients with active infective endocarditis resistant to medical treatment was 17%. Thus valve surgery is positively indicated in this group.

Hypercholesterolaemia and endothelium dependent vasomotor responses

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Experimental hypercholesterolaemia has been reported to enhance vasoconstrictor responses. One explanation might be reduced activity of endothelium derived relaxant factor. This possibility was explored with isolated aortic ring preparations from 20 week old rabbits (male New Zealand white) after free feeding with standard diet or diet enriched with 2% cholesterol for 10 weeks. Endothelium was removed from half the rings by gentle abrasion. Preparations were mounted isometrically in oxygenated Holman's solution at 37°C ($n \gg 23$ for each experiment). In control preparations, the maximum response to 5-hydroxytryptamine (5HT) was greater with endothelium than without (1526(SEM 109) *vs* 1251(82) mg, $p<0{\cdot}05$), shown previously to be due to basal endothelium derived relaxant factor activity. In hypercholesterolaemic preparations endothelium did not significantly affect the 5HT response. In neither control nor hypercholesterolaemic preparations did endothelium significantly alter maximum response or EC_{50} to ergometrine. Maximum responses to 5HT or ergometrine, with or without endothelium, did not differ between control and hypercholesterolaemic preparations, implying that smooth muscle constrictor responses were not altered by cholesterol feeding. Acetylcholine ($\geqslant 10^{-9}$ mol/l) induced, endothelium dependent relaxation, in preparations preconstricted with 5HT, was significantly greater in control than hypercholesterolaemic preparations (for example, at 10^{-6} mol/l, 70(5) *vs* 10(5)%, $p<0\cdot005$). This implies less endothelium derived relaxant factor activity in hypercholesterolaemic animals. Whether this reflects reduced reduction, release, activity, or penetration is unknown. Endothelium derived relaxant factor is unstable and increased diffusional distance could account for these observations. These observations are consistent with the possibility that atheroma may reduce endothelium derived relaxant factor activity and enhance constrictor responses in vivo.

A study of aspirin or sulphinpyrazone in unstable angina

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A randomised, double blind, placebo controlled trial of aspirin (acetyl salicylic acid) 325 mg four times daily or sulphinpyrazone 200 mg four times daily was carried out in 555 patients of either sex with unstable angina. Patients entered the trial within eight days of admission to the coronary care unit and were followed for up to two years (mean 19 months). Primary analysis of efficacy was based on cardiac death or non-fatal myocardial infarction in eligible patients who had not been off medication for 28 consecutive days preceding an outcome. There was no evidence of interaction between the two drugs; therefore outcomes were analysed separately for each drug. Aspirin reduced the number of cardiac deaths or non-fatal myocardial infarction by 55%, from 37 (13%) to 16 (6%) ($p=0\cdot004$). Sulphinryrazone produced no statistically significant effect with 27 events off the drug and 26 events on the drug. The total number of deaths was reduced by 70% by aspirin, from 22 (8%) to six (2%) ($p=0\cdot005$). Sulphinpyrazone reduced total deaths from 15 (5%) to 13 (5%) ($p=0\cdot329$). On the basis of an intention to treat analysis, aspirin reduced the number of cardiac deaths or non-fatal myocardial infarctions from 42 (15%) to 29 (11%), a risk reduction of 33% ($p=0\cdot053$), and reduced all deaths from 28 (10%) to 16 (6%), a risk reduction of 43% ($p=0\cdot036$). The observed benefits were similar for both sexes.

It is concluded that aspirin 325 mg four times daily results in a marked reduction of cardiac death or non-fatal myocardial infarction and of total mortality in patients hospitalised with unstable angina.

Practical aspects of ambulatory ST segment monitoring: comparison of frequency modulated and direct recording systems

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Ambulatory ST segment recording requires a low frequency range down to 0·05 Hz which has necessitated the use of frequency modulated systems (Oxford Medilog II, range 0·05–40 Hz at −3 dB). Recently a direct recording system (Reynolds Tracker TRIB, range 0·07–100 Hz at −3 dB) has been introduced and is widely used in clinical practice for arrhythmia monitoring. The purpose of this study is to determine whether the Reynolds system is reliable for ST segment monitoring in routine clinical practice. Twenty four hour ambulatory ST segment monitoring was performed concurrently on the Reynolds Tracker and Oxford Medilog II systems. Tapes were analysed at 60 times recorded speed and a trend of ST segments obtained with each system. Thirty episodes of transient ST depression ($\geqslant$1–3 mm) were recorded and their onset, duration, and maximum magnitude noted. On visual analysis, the Reynolds system detected 90% of episodes with one false positive. Visually the mean duration of episodes and the maximum magnitude of ST depression were similar using both systems. Using the trend analysis the Reynolds system was more accurate (26 out of 30 episodes) than the Oxford system (19 out of 30). The Oxford trend was more prone to artefacts and particularly inaccurate for ST depression >3 mm. The mean duration of the episodes detected by both trend systems was identical. Thus for routine clinical practice the Reynolds Tracker system was capable of detecting the majority of episodes of ST segment depression both visually and using the trend analysis with few false positives.

The "normal" ST segment: a study of ST variability in 105 healthy volunteers by ambulatory monitoring and exercise testing

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There is at present no definite consensus on the pattern of ST segment variability in healthy man. One hundred and five normal volunteers (36 women, 69 men, between the ages of 20–67 years) selected at random from the general population were studied. All underwent a clinical examination, an electrocardiogram, and questioning regarding their personal and family history. They then underwent ambulatory electrocardiographic monitoring for 24–48 hours (CM5 and CC5) using an Oxford Medilog II recorder, followed by a symptom limited treadmill exercise test. Simultaneous electrocardiograms during exercise were made on a fresh Medilog II tape, the signal being picked up from the same electrodes as the exercise system. The peak exercise heart rate achieved varied from 88% to 96% of the age predicted maximum, and eight subjects showed a positive ischaemic response and were excluded from the final analysis. Orthostatic testing was performed in all subjects. The J point shift on standing varied from a fall of 0·5 mm to a rise of 0·4 mm in 96% cases. Only five had a higher shift, with falls up to 0·9 mm and rises up to 0·8 mm. Validation of ambulatory ST recording was achieved by comparing ST changes with the Medilog and a computerised exercise system. The standard deviation of differences in ST segment was 0·2 mm for lead CM5 and 0·3 mm for CC5. Of the tapes analysed, 25% revealed episodes of significant abnormal ST depression, over half in subjects under 40 years and three quarters in men. All episodes of ST depression were related to increased heart rate, secondary to some activity. Very few cases showed ST elevation. This study defines the ST segment behaviour during normal life in healthy man and affords a standard with which to compare studies in disease.

Exercise induced ST depression before and immediately after successful left anterior descending coronary angioplasty

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Twenty four patients with single vessel left anterior descending coronary artery disease (22 males, mean age 52 years) had maximal stress tests one day before and three days after successful left anterior descending coronary angioplasty to investigate the pattern of exercise induced ischaemia due to left anterior descending artery disease detected by a 12 lead electrocardiogram and the immediate effects of angioplasty on reversible myocardial ischaemia and exercise variables. Twenty patients had exercise induced ST depression before angioplasty. The number of patients with ST depression in each lead was: 19, V5; 14, V6; 11, V4; 5, V3; 5, II; 0, V1, the remaining leads each detecting ST depression in one patient. Exercise induced angina and ST depression occurred in 16 and 20 patients respectively before angioplasty and in five ($p<0{\cdot}01$) and 10 ($p<0{\cdot}01$) after the procedure. There was a significant increase in the mean maximal exercise duration after angioplasty (15·7(SD 7·5) min) compared with the value before angioplasty (12·0(3·7) min $p<0{\cdot}001$), but there were no significant changes in mean maximal heart rate or in the maximal rate pressure product.

It is concluded that (*a*) reversible ischaemia due to left anterior descending coronary artery disease is best detected by leads V5 and V6 and not by the septal leads during stress testing, (*b*) features of reversible ischaemia and exercise duration are signficantly improved immediately after successful angioplasty, and (*c*) ST depression on exercise may persist immediately after angioplasty defined as a primary success.

ST segment changes during left anterior descending coronary angioplasty: the significance of reciprocal changes

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There is debate about the significance of inferior ST segment changes in patients with anterior myocardial infarction. At angioplasty continuous six lead (I, II, III, V2, V5, and CM5) surface electrocardiograms were recorded during balloon inflation in the left anterior descending coronary artery. Nine patients with single left anterior descending coronary artery disease and eight patients with significant stenoses also in the circumflex or the right coronary arteries or both were studied. ST segment changes were measured with a magnifying lens to an accuracy of 0·1 mm. In patients with isolated left anterior descending artery disease, occlusion resulted in ST elevation in V2 in all nine patients (0·8–5·1 mm) and was first observed in this lead in six (mean duration 14(12)s). Reciprocal ST depression occurred in lead III in seven patients, and one patient each had ST elevation and no ST change. In patients with multivessel disease and left anterior descending artery occlusion, V2 showed ST depression in four and ST elevation in four, whereas lead III had ST depression only. In 15 of the 17 patients, occlusion of left anterior descending artery resulted in inferior ST segment depression. In seven patients with isolated left anterior descending artery disease, these changes are likely to be reciprocal. Thus, the presence or timing of inferior ST segment changes in the event of left anterior descending artery occlusion do not signify presence or absence of disease in other vessels.

Computed tomographic assessment of intracardiac thrombus

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Thirty eight patients with clinical conditions associated with intracardiac thrombus formation were studied by computed tomography and cross sectional echocardiography within a seven day period. Computed tomographic scans were performed during intravenous infusion of contrast medium at 1 cm intervals to image the appropriate cardiac chambers. Cross sectional echocardiography was performed in long and short axis and apical four chamber views. Echocardiography identified five cases of left ventricular and one right atrial thrombus. Computed tomography also demonstrated these cases, and in addition identified a further eight left ventricular and eight left atrial filling defects having the same appearances as in those cases in which echocardiography had identified a thrombus. Coincidental left ventricular angiography confirmed the presence of left ventricular filling defect in three of the eight cases identified by computed tomography alone. Measurement of thrombus density at computed tomography showed a significant difference in density ($p<0{\cdot}02$) between those cases suspected of having new thrombus (for example, myocardial infarct) and those with organised thrombus.

These results suggest that computed tomography is an accurate method for identifying intracardiac thrombus and for differentiating new from organised thrombus. In addition, it may be a useful technique in those cases in which echocardiography is unhelpful.

The heart in middle aged first time marathon runners

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Marathon running continues to increase in popularity, though in older untrained subjects there is concern about its effect on the cardiovascular system. Forty one previously unfit middle aged men (mean age 43(2) range 35–50 years) who underwent a structured training programme involving 3·5 hours running by 15 weeks training rising to 8 hours per week after 30 weeks were recruited. Cardiac function was assessed by first pass radionuclide ventriculography at rest and at maximum exercise in 15 subjects using the short lived isotope gold-195m. Left ventricular ejection fraction rose from 59(5)% to 66(7)% ($p<0{\cdot}01$) before and from 61(7)% to 70(6)% ($p<0{\cdot}005$) and 59(8)% to 70(8)% ($p<0{\cdot}005$) after 15 and 30 weeks training. Exercise ejection fraction was significantly higher after training ($p<0{\cdot}05$). Resting end diastolic volume did not change (150(32), 156(26), and 160(31) EDV units). In 10 subjects cardiac function was assessed by gated radionuclide ventriculography. A mobile gammacamera positioned at the finish enabled a postmarathon scan to be performed within 30 minutes of finishing. Left ventricular ejection fraction was 54(6)% before, 61(9)% and 62(9)% after training, and was maintained postmarathon at 63(11)%; regional wall motion analysis was normal, and moreover no significant electrocardiographic change occurred in any of study group ($n=30$). Thus training for the marathon increased left ventricular ejection fraction response to exercise at an early stage in training, and no adverse effect on cardiac function was evident immediately after the race.

Stress induced right ventricular dysfunction: an indication of reversible right ventricular ischaemia

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Stress induced changes in left ventricular ejection fraction are widely used in the detection and assessment of coronary artery disease. This study demonstrates that right ventricular ischaemia may also occur and assesses its significance in terms of coronary artery anatomy. Fourteen normal subjects and 26 with coronary artery disease were studied by equilibrium radionuclide ventriculography at rest and during maximal dynamic exercise. Right ventricular ejection fraction was calculated from count changes within a right ventricular region of interest after functional background subtraction. Mean normal resting right ventricular ejection fraction was 0·42 (SD 0·13) and all normal subjects increased right ventricular ejection fraction with stress (mean difference +0·13 (SD 0·10)). Mean difference in right ventricular ejection fraction in the subjects with coronary artery disease was significantly lower at 0·00 (SD 0·08), but there was overlap between the two groups. The largest falls in right ventricular ejection fraction were, however, seen if there was severe disease of both right coronary and left anterior descending coronary arteries or if there was right coronary artery occlusion without retrograde filling. In this subgroup with the most severely compromised right ventricular perfusion (11 subjects) right ventricular ejection fraction always fell with stress, and mean difference in right ventricular ejection fraction was −0·07 (SD 0·05). There was no significant correlation between the mean differences in left ventricular and right ventricular ejection fractions, implying that the right ventricular dysfunction was due to right ventricular ischaemia rather than secondary to left ventricular dysfunction. Stress induced right ventricular ischaemia can therefore be detected readily by radionuclide ventriculography.

Withering Commemoration Symposium

The following are abstracts of papers that were presented on Thursday 18 April 1985, at the joint meeting of the Association of Physicians and British Cardiac Society, to commemorate the bicentenary of the publication of William Withering's "An Account of the Foxglove." Other papers on digitalis will appear in a later issue.

Pharmacology of digoxin

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Among the interesting facets of the pharmacology of the cardiac glycosides are the origins of the distinctly different clinical practices in the use of digoxin extant in the United Kingdom and the United States. These can be traced in large part to the patterns established by Sir James Mackenzie and Henry Christian in the early twentieth century. Current areas of active research interest considered include the basic mechanism(s) of digitalis action at the cellular level, which were discussed in this lecture chiefly in terms of sarcolemmal sodium pump inhibition and its consequences. Pharmacokinetics and bioavailability were touched on briefly, with comments on the clinical use of serum digoxin concentrations. Finally, an update was provided on the reversal of advanced life threatening digitalis toxicity with purified digoxin specific Fab fragments. Sixty three patients have been treated, of whom 33 ingested digoxin accidentally or with suicidal intent. Digoxin specific Fab doses were calculated to be equimolar to the body burden of cardiac glycoside. The onset of reversal of toxicity was within 30 minutes in most cases; free serum digoxin concentrations were undetectable within minutes of Fab administration. Digoxin induced hyperkalemia was reversed in all 29 patients presenting with this abnormality. Among 56 patients meeting criteria for advanced digitalis toxicity who were not yet agonal when treated, 53 responded positively and 52 had full resolution of toxicity. No obvious adverse reactions to treatment were observed.

Modern views on myocardial contractility

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The structures of the contractile and regulatory systems of cardiac muscle are very similar to those of skeletal muscle but are composed of proteins, the synthesis of which are controlled by genes that are uniquely expressed in the heart. The general metabolic processes involved in adenosine triphosphate production in cardiac muscle are fairly well understood and knowledge of them is used in clinical practice. Important advances have been made in the development of nuclear magnetic resonance techniques for non-invasively determining metabolic levels in the intact working heart and hence monitoring its function. Energy transduction in the heart is almost certainly very similar to that of other muscles, but the precise mechanism still remains uncertain despite intensive research. The regulation of contractile activity is of special significance to the myocardium, and recent investigations have detected aspects that are unique to cardiac muscle.

Digitalis and membranes

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The cardiotonic steroids are specific inhibitors of the membrane sodium-potassium activated adenosine triphosphatase responsible for the electrogenic exchange of sodium for potassium ions. One of the first actions of digitalis therefore is to perturb the surface membrane current. These current changes and their correlation with tension changes have been well characterised in recent work. Above 10^{-7} mol/l, strophanthidin reduces outward membrane current and increases the force of contraction. At lower concentrations, however, the drug can *increase* the pump current and this may be associated *either* with a reduction in force *or* with an increase in force.

Membrane current changes also occur as a secondary consequence of changes in pump activity either as a result of changes in electrochemical gradients or in the form of the "transient inward" current that may underlie glycoside induced arrhythmia. It has now become possible to reconstruct these and other glycoside induced changes using a computer model of electrical activity and calcium sequestration.

Digitalis for arrhythmias

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Excellent anecdotal evidence suggests that some of the original patients given digitalis by Withering and his contemporaries responded in exactly the same fashion as was later shown to be the case when, more than a century later, atrial fibrillation was recognised and the value of digitalis in controlling the ventricular rate by influencing atrioventricular nodal conduction demonstrated. Subsequently, it was shown to help block atrioventricular nodal conduction in atrial flutter but on some occasions to cause the return of sinus rhythm, often through a transient phase of atrial fibrillation. More than 50 years ago, digitalis preparations given intravenously were shown sometimes to terminate supraventricular arrhythmias, and it became widely used for this purpose. Its relative success rate is, however, low in comparison with more recently developed agents, especially some calcium antagonists, but it is potentially valuable, either alone or in combination with other agents, in the prophylaxis of re-entry atrioventricular tachycardias. Its greatest value is when given orally in atrial fibrillation in order to slow conduction through the atrioventricular node, where it has not been usurped by other agents; it is, however, contraindicated when atrial fibrillation complicates pre-excitation.

Digitalis toxicity

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Clinical manifestations of digitalis toxicity were clearly described by Withering. One hundred years later certain digitalis induced arrhythmias were inscribed on the smoked drum, the polygraph, and shortly thereafter, with the introduction of the electrocardiograph, manifestations of digitalis toxicity as recognised today were recorded in animal and man.

With popularisation of the direct writing electrocardiograph in the late 'forties and the introduction of digitoxin in recommended doses that in retrospect appear inappropriately high, the documented prevalence of digitalis toxicity rose rapidly. With increased understanding of the interaction of electrolytes and digitalis and perhaps, but more importantly, the widespread use of digoxin in doses derived largely from its inotropic action and thus inappropriately low for the management of many of arrhythmias, the prevalence of toxicity began to decline. In addition, the advent of serum concentrations and the widespread acceptance of the concept of "therapeutic" concentrations, which frequently fall short of the desired clinical endpoint, served to preclude digitalis toxicity.

With the decline in digitalis toxicity as a result of the above factors, some of the digitalis related arrhythmias that once were common are now rarely observed. This discussion focused on arrhythmias which are highly specific for digitalis toxicity and are less commonly encountered. The discussion and classification of the arrhythmias are based on their most probable electrophysiological mechanism.

Unfortunately, Dr Fisch was unable to present his paper on account of ill health.

Br Heart J 1985; 53: 688–9

Correspondence

Lead specificity of the maximum ST/heart rate slope response

Sir,

The letter by Beattie *et al* (1984; 53: 349) contains some interesting and remarkable statements, and a few are worthy of comment. The letter states that "the maximum rate of change of ST amplitude was a poor predictor of the extent of coronary artery disease" when using "a computerised Frank orthogonal lead system." This finding is hardly surprising; though the full details of the protocols have not been stated, it seems that this report is yet another that has used methods different from those used in the Leeds test and obtained different results. In Leeds the ST/HR slope, using conventional leads plus lead CM5, gives results after manual measurement that are still consistent with our initial experience; the maximal ST/HR slope is an accurate index of the presence and severity of myocardial ischaemia, which in the patients with anginal pain is assessed and graded according to results of coronary arteriography.

A remarkable feature of the letter on the use of the maximal ST/HR slope is the suggestion that this "assumes that the ST response to exercise is uniform in all leads and that a common pathophysiological mechanism—namely a mismatch of myocardial oxygen supply and demand—is the sole determinant of such a response." Then the letter proceeds to destroy its own suggestion, using the well accepted contention that electrocardiographic changes are influenced by the region of the myocardium in which ischaemia occurs.

Perhaps we might be allowed to state that in our use of the maximal ST/HR slope there is no need for any assumptions to be made; but there are implications of the results. Also our up to date experience with the maximal ST/HR slope is that this slope is an index of myocardial ischaemia; it is still accurate in detecting the ischaemia as assessed by coronary angiography in a selected group of patients with angina, but it seems also in ongoing trials to be an index of myocardial ischaemia in patients without coronary constriction, for example, in patients with a dilated or hypertrophied left ventricle.

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Radiographic contrast agents in angiocardiography

Sir,

Hayward and Dawson are to be congratulated on their excellent review of radiographic contrast agents in angiocardiography (1984; 52: 361–8). Their statement that "the viscosities of the new agents are all appreciably higher than those of conventional agents" is, however, at variance with their Table, which says that Niopam 370 is less viscous than Urografin 370 at 37°C. It is my impression that higher viscosity limits the delivery of contrast medium during hand injections, as for coronary angiography, but that for really high rates of delivery the degree of turbulence of flow in the catheter is more important. This means that for pump injections the length and internal diameter of the catheter are more critical to delivery than the viscosity of the contrast medium.

At present, most cardiac investigations are performed without serious side effects using ionic media. The routine use of these expensive newer media can be justified only in certain subgroups of patients—for example, in pulmonary angiography, paediatric angiocardiography, and in combined coronary/carotid examinations. The new media should be made available in every department for occasional use in high risk adult patients. On occasions, however, it may become apparent during a procedure that the patient is showing adverse haemodynamic or electrocardiographic responses to an ionic medium, and it would be an advantage to be able to change to a low osmolality medium during such a procedure. I and my colleagues at this hospital have studied a number of patients for whom a change was made from ionic to another medium. In a series of 100 patients in whom iopamidol (Niopam) was given for the left ventriculogram, after coronary angiography with Urografin 370, three patients experienced some degree of nausea, no patient vomited or retched, and there was no incidence of any haemodynamic deterioration. We have concluded that iopamidol may be safely substituted for Urografin 370 during a procedure.

The findings compare with our other series in which the same sequence using Hexabrix instead of iopamidol resulted in a 7·8% incidence of nausea and a 6·7% incidence of vomiting.[1]

J B Partridge
Department of Radiology,
Prince Charles Hospital,
Chermside,
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Australia.

Reference

1 Partridge JB. Patient tolerance to sequential administration of Urografin and Hexabrix [Letter]. *Br J Radiol* 1985; 58: 272.

This letter was shown to the authors, who reply as follows:

Sir,

We are grateful to Dr Partridge for his comments, with which we are in complete agreement. When discussing viscosity in our paper we sought to make the point that at equal iodine concentrations the new agents have significantly higher viscosities than the generality of conventional contrast agents. In the particular specific case of Niopam 370 and Urografin 370, however, Dr Partridge quite correctly points out that there is practically no viscosity difference, as indeed our Table shows.

Our department adopts Dr Partridge's approach of using a new contrast agent only in selected patients in all radiological procedures requiring an intravascular contrast agent, and it is our impression that most other departments in the United Kingdom adopt this sensible approach. Grainger has made a useful summary of criteria for the selection of such patients.[1] As for cardiac radiology in particular, most practitioners in the United Kingdom appear to take the reasonable view that, in good hands, the incidence of serious complications is low and that, though they undoubtedly have strong theoretical advantages, the general use of the new agents is at the moment unjustified on economic grounds. While savings should be made wherever possible without detrimental effect on patients it is pertinent to make the point that the cost of the contrast material, old or new, is only a very small proportion of the total cost of a cardiac study.

Peter Dawson,
Roger Hayward,
Department of Radiology,
Middlesex Hospital,
London W1N 8AA.

Reference

1 Grainger RG. The clinical and financial implications of the low osmolar radiological contrast media [Letter]. *Clinical Radiology* 1984; 35: 251–2.

Notices

Management of cardiac arrhythmias

An international conference on the management of cardiac arrhythmias organised by the British Heart Foundation will be held in London from 2 to 4 September 1987. Further details may be obtained from the Organising Committee, British Heart Foundation, 102 Gloucester Place, London W1H 4DH.

Travelling fellowship

The Royal College of Physicians and the British Cardiac Society have created a travelling fellowship to enable a senior cardiologist from abroad to visit this country for a few weeks. The chief purpose of this fellowship is to provide the opportunity for contact with specialist colleagues and societies that may not be available in the fellow's own country; it is restricted to physicians from the Third World. The first holder of the fellowship is Dr Waldo Fernandez, associate professor of medicine in the Universidad San Marcos, Lima, Peru. He spent six weeks in March and April visiting centres in London, Oxford, Cambridge, and Birmingham where he attended the Spring Meeting of the British Cardiac Society.

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts will be 2 January 1986.

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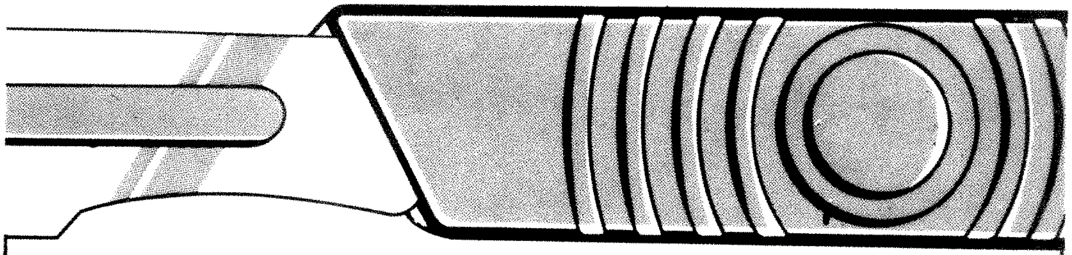

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TENORMIN LS FOR MILD AND OLDER HYPERTENSIVES

'Tenormin' and 'Tenormin' LS Prescribing Notes

PRESENTATION: 'Tenormin' tablets containing atenolol 100mg are round, bi-convex, orange and film coated. 'Tenormin' LS tablets containing atenolol 50mg are round, bi-convex, orange and film coated.
USES: Management of Hypertension.
DOSAGE: 'Tenormin' 100mg orally once a day and 'Tenormin' LS orally once a day; some patients may respond adequately to 'Tenormin' low strength.
CONTRA-INDICATIONS: Heart Block.
PRECAUTIONS: Untreated cardiac failure, bradycardia, renal failure, anaesthesia, pregnancy. Caution in patients with chronic obstructive airways disease or asthma. 'Tenormin' modifies the tachycardia of hypoglycaemia. Co-administration of verapamil or Class I antidysrhythmic agents. Withdrawal of clonidine. Withdrawal of beta-blocking drugs should be gradual in patients

SIDE EFFECTS: Coldness of extremities, bradycardia and muscular f
may occur. Sleep disturbance rarely seen. Rashes and dry eyes have be
reported with beta-blockers–consider discontinuance if they occur.
PACK SIZE AND BASIC NHS COST: 'Tenormin' 28's £6.98; 'Tenormin' L
28's £4.88.
PRODUCT LICENCE NUMBER: 'Tenormin' 29/122; 'Tenormin' LS 29/8

'Tenormin', 'Tenormin' LS are trademarks.

Full prescribing information is available on request to the Co
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